```
Set      Items   Description
S1      510825   ENHANC?()AGENT? OR DMSO OR ETHANOL OR PENETRAT?()SOLVENT? -
            OR (SULPHUR? OR SULFUR?)()COMPOUND?()SOLVENT?
S2       29447   RN=67-68-5
S3           0   DC=D.02.886.640.150
S4     1151003   (CLARIFY? OR CLARIFI?)()AGENT? OR GLUCOSE OR GLUCONIC OR D-
            EXTROGLUCOSE OR DEXTROSE OR DEXTRONIC OR MALTONIC
S5      368002   GLYCOGEN? OR GLYCERYL? OR GLYCERIN? OR GLYCEROL?
S6           0   DC=D09.203.546.359.448
S7      324444   RN=50-99-7
S8        6276   DIATRIZOATE()MEGLUMINE OR DIATRIZOATE()METHLYGLUCAMINE OR -
            DIATRIZOIC()ACID()METHYLGLUCAMINE OR MEGLUMINE()DIATRIZOATE OR
             METHYLGLUCAMINE()DIATRIZOATE OR (AMIDOTRICOIC OR AMIDOTRIZOI-
            C)()ACID? OR MEGLUMINE()AMIDOTRIZOATE
S9        5410   RN=131-49-7
S10          0   DC=(D02.033.800.813.550.500 OR D02.241.223.100.140.100.375-
            .880.275 OR D09.203.037.342.600.500 OR D09.203.853.813.550.50-
            0)
S11      54642   IONTOPHORE? OR IONTOTHERAP? OR IONIC()THERAP? OR EMDA OR S-
            ONOPHORE? OR ELECTROPORAT? OR ELECTRO()PORAT?
S12          0   DC=E05.300.650
S13         42   (MICRONEEDLE? OR MICRO()NEEDLE?)()ARRAY? ?
S14   13934886   INCREAS? OR ENHANC? OR AMELIORAT?
S15    3892039   PERMIT? OR PERMISS? OR ALLOW?
S16    6121599   BETTER? OR IMPROV?
S17     669461   RECEPTABIL? OR PERMEABIL? OR PERMEABL? OR LUCENCY?
S18     260617   TRANSLUCEN? OR TRANSPAREN? OR CLEARNESS OR CLARITY
S19    5381045   OPTICAL? OR LIGHT? OR LUCID?
S20    1581333   PERMEAB?()(BARRIER? OR LAYER? OR STRAT?) OR SKIN
S21    1311267   CONJUNCTIV? OR EPITHELI? OR SCLERA? OR STRAT?()CORNE? OR (-
            INTERSTIT? OR INTER()STIT?)()(SPACE? OR TISSUE?)
S22        210   IC=(A61N? OR A61M? OR A61B?)
S23      52703   DIMETHYL()(SULFOXIDE OR SULPHONYL) OR DIMEXIDE OR RIMSO OR
            RIMSO100 OR SULFINYL()BISMETHANE OR SULFINYLBISMETHANE
S24     405753   (DRIVING OR ELECTRIC?()PULSE OR ELECTRICPULSE OR ELECTROMO-
            TIVE OR ELECTRO()MOTIVE OR ACOUSTIC? OR ULTRASONIC? OR ELECTR-
            ICAL? OR RADIOFREQUENCY? OR RADIO()FREQUENCY? OR TEMPERATURE -
            OR THERMAL OR PHYSICAL OR CHEMICAL OR CONCENTRATION OR...
S25        199   (S1:S3 OR S23) AND S4:S10 AND (S11:S13 OR S24)
S26        139   S25 AND S14:S22
S27         37   S26 AND S20:S21
S28         37   S25 AND S20:S21
S29         37   S27:S28
S30         19   S29 AND PY<1999
S31         16   RD (unique items)
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File 99:Wilson Appl. Sci & Tech Abs 1983-2003/Oct
(c) 2003 The HW Wilson Co.

31/5,K/1 (Item 1 from file: 5)
DIALOG(R)File 5:Biosis Previews(R)

0009529125 BIOSIS NO.: 199497550410
Effect of chemical enhancers **and conducting gels on** iontophoretic **transdermal delivery of cromolyn sodium**
AUTHOR: Gupta Sanjeev K (Reprint); Kumar Saran; Bolton Sanford; Behl Charanjeet R; Malick A Waseem
AUTHOR ADDRESS: Res. Dev., Barr Lab. Inc., 2 Quaker Road, Pomona, NY 10970, USA**USA
JOURNAL: Journal of Controlled Release 31 (3): p229-236 1994 **1994**
ISSN: 0168-3659
DOCUMENT TYPE: Article
RECORD TYPE: Abstract
LANGUAGE: English

ABSTRACT: In vitro **iontophoretic** transdermal delivery (ITD) at a continuous current density of 0.1 mA/cm-2 of cromolyn sodium (CS) across hairless guinea pig **skin** (HGP) was studied with and without **enhancers** . CS was quantitated by a sensitive HPLC method. At a saturated drug concentration of CS in 80:20 mixture of **ethanol** : 6.66 mM acetate buffer, an overall flux **enhancement** compared to buffer alone was observed. This **enhancement** was determined to be an additive effect of **iontophoresis** and **ethanol** . Chemical **enhancers** , such as anionic surfactants (e.g. sodium dodecyl sulfonate and sodium lauryl sulfate), inhibited the permeation of CS ions at concentration less than or equal to the critical micelle concentration. No significant change in flux (P gt 0.05) was observed when propylene glycol was added at different concentrations to yield solutions with varying dielectric constants in the aqueous donor medium. Aqueous **glycerol** solution was ineffective for ITD. Conducting gels of ionic polymers, polyjel-HV and lubrijel-MS, decreased the flux of CS significantly (P lt 0.05). Non-ionic polymers such as hydroxypropyl cellulose (Klucel-LF) and polyvinyl alcohol did not affect the flux and may be used for ITD of CS from a transdermal patch. An optimized solution formulation for CS was incorporated in a commercially available electropatch, from which delivery rates up to 46 +- 5 mu-g/cm-2hr-1, were achieved. The optimized formulation of CS provided about 18 fold higher flux compared to an unoptimized formulation from the electropatch. Stainless steel or Ag/AgCl electrodes showed no difference in the flux of CS from the patch. Therapeutic levels of CS in humans may be achieved by this modern non-invasive drug-delivery route.

REGISTRY NUMBERS: 15826-37-6: CROMOLYN SODIUM
DESCRIPTORS:
MAJOR CONCEPTS: Biochemistry and Molecular Biophysics; Integumentary System--Chemical Coordination and Homeostasis; Metabolism; Pharmacology ; Physiology
BIOSYSTEMATIC NAMES: Caviidae--Rodentia, Mammalia, Vertebrata, Chordata, Animalia; Hominidae--Primates, Mammalia, Vertebrata, Chordata, Animalia ; Mammalia--Vertebrata, Chordata, Animalia
ORGANISMS: guinea-pig (Caviidae); human (Hominidae); mammal (Mammalia)
COMMON TAXONOMIC TERMS: Rodents; Humans; Primates; Animals; Chordates; Mammals; Nonhuman Vertebrates; Nonhuman Mammals; Vertebrates
CHEMICALS & BIOCHEMICALS: CROMOLYN SODIUM
MISCELLANEOUS TERMS: DELIVERY RATES; DRUG DELIVERY SYSTEM; ELECTRODES; ELECTROPATCH; FLUX; METHODS; PHARMACEUTICALS
CONCEPT CODES:
01006 Methods - Laboratory apparatus
04500 Mathematical biology and statistical methods

10010 Comparative biochemistry
10050 Biochemistry methods - General
10060 Biochemistry studies - General
10069 Biochemistry studies - Minerals
10502 Biophysics - General
12002 Physiology - General
12003 Physiology - Comparative
13002 Metabolism - General metabolism and metabolic pathways
18504 Integumentary system - Physiology and biochemistry
22003 Pharmacology - Drug metabolism and metabolic stimulators
22005 Pharmacology - Clinical pharmacology
22030 Pharmacology - Respiratory system
22100 Routes of immunization, infection and therapy
BIOSYSTEMATIC CODES:
86300 Caviidae
86215 Hominidae
85700 Mammalia

Effect of chemical enhancers **and conducting gels on** iontophoretic **transdermal delivery of cromolyn sodium**
1994

ABSTRACT: In vitro **iontophoretic** transdermal delivery (ITD) at a continuous current density of 0.1 mA/cm-2 of cromolyn sodium (CS) across hairless guinea pig **skin** (HGP) was studied with and without **enhancers** . CS was quantitated by a sensitive HPLC method. At a saturated drug concentration of CS in 80:20 mixture of **ethanol** : 6.66 mM acetate buffer, an overall flux **enhancement** compared to buffer alone was observed. This **enhancement** was determined to be an additive effect of **iontophoresis** and **ethanol** . Chemical **enhancers** , such as anionic surfactants (e.g. sodium dodecyl sulfonate and sodium lauryl sulfate), inhibited the...

...different concentrations to yield solutions with varying dielectric constants in the aqueous donor medium. Aqueous **glycerol** solution was ineffective for ITD. Conducting gels of ionic polymers, polyjel-HV and lubrijel-MS...

31/5,K/2 (Item 1 from file: 34)
DIALOG(R)File 34:SciSearch(R) Cited Ref Sci

05774444 Genuine Article#: WX213 Number of References: 49
Title: Ultrastructural characterization of sulfur mustard-induced vesication in isolated perfused porcine skin
Author(s): MonteiroRiviere NA (REPRINT) ; Inman AO
Corporate Source: N CAROLINA STATE UNIV,CTR CUTANEOUS PHARMACOL & TOXICOL, 4700 HILLSBOROUGH ST/RALEIGH//NC/27606 (REPRINT)
Journal: MICROSCOPY RESEARCH AND TECHNIQUE, **1997** , V37, N3 (MAY 1), P 229-241
ISSN: 1059-910X Publication date: 19970501
Publisher: WILEY-LISS, DIV JOHN WILEY & SONS INC, 605 THIRD AVE, NEW YORK, NY 10158-0012
Language: English Document Type: ARTICLE
Geographic Location: USA
Subfile: CC LIFE--Current Contents, Life Sciences; CC ENGI--Current Contents, Engineering, Computing & Technology
Journal Subject Category: MICROSCOPY; BIOLOGY
Abstract: The isolated perfused porcine **skin** flap (IPPSF) is a novel

alternative, humane in vitro model consisting of a viable epidermis and dermis with a functional microvasculature. For this study, 200 mu l of either 10.0, 5.0, 2.5, 1.25, 0.50, or 0.20 mg/ml of bis (2-chloroethyl) sulfide (HD) in **ethanol** or **ethanol** control was topically applied to a 5.0 cm(2) dosing area of the IPPSF and perfused for 8 h with recirculating media. HD dermatotoxicity was assessed in the flap by cumulative **glucose** utilization (CGU), vascular resistance (VR), **light** microscopy (LM), scanning electron microscopy (SEM), and transmission electron microscopy (TEM). HD produced a statistically significant dose relationship for gross blisters and microvesicles. The HD-treated IPPSFs were also characterized by a decrease in CGU and an **increase** in VR. **Light** microscopic changes included mild intracellular and slight intercellular epidermal edema, multifocal epidermal-dermal separation, and dark basal cells. Ultrastructural alterations consisted of cytoplasmic vacuoles, pyknotic basal cells, nucleolar segregation, and epidermal-dermal separation occurring between the lamina **lucida** and lamina densa of the basement membrane. The severity of these changes **increased** in a dose-dependent manner. Morphologically, the IPPSF appeared similar to human **skin** exposed to HD with the formation of macroscopic blisters and microscopic vesicles. In conclusion, the IPPSF appears to be an appropriate in vitro model with which to study the pathogenesis of vesicant-induced toxicity. (C) Wiley-Liss, Inc.

Descriptors--Author Keywords: microvesicle ; blisters ; sulfur mustard (bis(2-chloroethyl) sulfide) ; isolated perfused **skin** ; vesication ; histology ; in vitro ; **skin** ; toxicology ; pig ; ultrastructure

Identifiers--KeyWord Plus(R): LESIONS PRODUCED INVIVO; ATHYMIC NUDE-MICE; PERCUTANEOUS-ABSORPTION; ORGAN-CULTURE; RABBIT **SKIN** ; INFLAMMATORY MEDIATORS; LIDOCAINE **IONTOPHORESIS** ; CUTANEOUS TOXICOLOGY; SERUM-PROTEIN; INVITRO MODEL

Research Fronts: 95-1958 001 (PORCINE **SKIN** ; PERCUTANEOUS-ABSORPTION OF TOPICAL PARATHION; SULFUR MUSTARD VAPOR)
95-8217 001 (SULFUR MUSTARD; HAIRLESS GUINEA-PIG **SKIN** ; INACTIVATION OF MICROSOMAL CA2+-ATPASE)

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WILLEMS JL, 1989, V3, P1, ANN MED MILITARIS BE
WILLIAMS PL, 1990, V79, P305, J PHARM SCI

Title: Ultrastructural characterization of sulfur mustard-induced vesication in isolated perfused porcine skin
, **1997**

Abstract: The isolated perfused porcine **skin** flap (IPPSF) is a novel alternative, humane in vitro model consisting of a viable epidermis...

...25, 0.50, or 0.20 mg/ml of bis (2-chloroethyl) sulfide (HD) in **ethanol** or **ethanol** control was topically applied to a 5.0 cm(2) dosing area of the IPPSF...

...for 8 h with recirculating media. HD dermatotoxicity was assessed in the flap by cumulative **glucose** utilization (CGU), vascular resistance (VR), **light** microscopy (LM), scanning electron microscopy (SEM), and transmission electron microscopy (TEM). HD produced a statistically...

...microvesicles. The HD-treated IPPSFs were also characterized by a decrease in CGU and an **increase** in VR. **Light** microscopic changes included mild intracellular and slight intercellular epidermal edema, multifocal epidermal-dermal separation, and...

...cytoplasmic vacuoles, pyknotic basal cells, nucleolar segregation, and epidermal-dermal separation occurring between the lamina **lucida** and lamina densa of the basement membrane. The severity of these changes **increased** in a dose-dependent manner. Morphologically, the IPPSF appeared similar to human **skin** exposed to HD with the formation of macroscopic blisters and microscopic vesicles. In conclusion, the...

...Identifiers--LESIONS PRODUCED INVIVO; ATHYMIC NUDE-MICE; PERCUTANEOUS-ABSORPTION; ORGAN-CULTURE; RABBIT **SKIN** ; INFLAMMATORY MEDIATORS; LIDOCAINE **IONTOPHORESIS** ; CUTANEOUS TOXICOLOGY; SERUM-PROTEIN; INVITRO MODEL

Research Fronts: 95-1958 001 (PORCINE **SKIN** ; PERCUTANEOUS-ABSORPTION OF TOPICAL PARATHION; SULFUR MUSTARD VAPOR)

95-8217 001 (SULFUR MUSTARD; HAIRLESS GUINEA-PIG **SKIN** ; INACTIVATION OF MICROSOMAL CA2+-ATPASE)

31/5,K/3 (Item 2 from file: 34)
DIALOG(R)File 34:SciSearch(R) Cited Ref Sci

05414464 Genuine Article#: VW731 Number of References: 24
Title: COMBINED EFFECT OF ULTRASOUND AND CHEMICAL ENHANCERS ON THE SKIN PERMEATION OF AMINOPYRINE
Author(s): UEDA H; ISSHIKI R; OGIHARA M; SUGIBAYASHI K; MORIMOTO Y
Corporate Source: JOSAI UNIV,FAC PHARMACEUT SCI,1-1 KEYAKIDAI/SAKADO/SAITAMA 35002/JAPAN/; JOSAI UNIV,FAC PHARMACEUT SCI/SAKADO/SAITAMA 35002/JAPAN/; JOSAI UNIV,LIFE SCI RES CTR/SAKADO/SAITAMA 35002/JAPAN/
Journal: INTERNATIONAL JOURNAL OF PHARMACEUTICS, 1996 , V143, N1 (OCT 25) , P37-45
ISSN: 0378-5173
Language: ENGLISH Document Type: ARTICLE
Geographic Location: JAPAN
Subfile: SciSearch; CC LIFE--Current Contents, Life Sciences
Journal Subject Category: PHARMACOLOGY & PHARMACY
Abstract: The combined effect of 150 kHz ultrasound with 111 mW/cm(2) intensity and chemical **enhancers** on the **skin** permeation of aminopyrine (AMP) was investigated using excised hairless rat **skin** . Monoterpenes (L-menthol, L-calvone and D-limonene), laurocapram (Azone(R)), **glycerol** monocaprylate (Sefsol-318(R)), isopropyl myristate and **ethanol** were selected as **enhancers** . Combined application of ultrasound and **enhancers** **increased** the **skin** permeation rate (flux) of AMP compared with ultrasound or **enhancers** alone. **Better** effects were obtained by the combination with monoterpenes. The influence of detailed conditions of ultrasound and **enhancer** applications on the AMP flux was further investigated using L-menthol. The **enhancement** effect by this combination was **increased** with an **increase** in ultrasonic application duration and L-menthol concentration, suggesting that these conditions might be used to achieve the controlled drug delivery. A pretreatment experiment with ultrasound or L-menthol was carried out, and L-menthol content in the **skin** and the **skin** permeation of deuterium oxide (D2O), used as a donor vehicle, were measured to understand the role of ultrasound in the combined effect. Application of ultrasound to the L-menthol-pretreated **skin** **increased** the AMP flux, while the effect of L-menthol on ultrasonic-pretreated **skin** was similar to that of L-menthol alone. The ultrasound **increased** the L-menthol content in the **skin** as well as the **skin** permeation of D2O from a vehicle with L-menthol. These results suggested that simultaneous application of ultrasound and **enhancers** is essential to obtain the pronounced effect. Ultrasound application also strongly assisted migration of L-menthol into **skin** , which **increases** the **enhancing** action on the **skin** permeation for a drug.
Descriptors--Author Keywords: **SKIN** PENETRATION **ENHANCEMENT** ; PHONOPHORESIS ; ULTRASOUND ; CHEMICAL **ENHANCERS** ; L-MENTHOL ; COMBINED EFFECT
Identifiers--KeyWords Plus: HAIRLESS RAT; PENETRATION; **ETHANOL**; ABSORPTION; INVITRO
Research Fronts: 94-0613 001 (WATER SONOLUMINESCENCE; SONOCHEMICAL DESTRUCTION; CAVITATION BUBBLE; DILUTE AQUEOUS-SOLUTION; OSCILLATORY PRESSURE FIELD; TRANSIENT CAVITY)
94-1427 001 (**SKIN** PENETRATION **ENHANCERS** ; **IONTOPHORETIC** TRANSDERMAL DELIVERY; FAPG BASE; PERCUTANEOUS PERMEATION; LUTEINIZING-HORMONE-RELEASING HORMONE (LHRH) IN-VITRO)
Cited References:

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WILLIAMS AC, 1991, V8, P17, PHARMACEUT RES

Title: COMBINED EFFECT OF ULTRASOUND AND CHEMICAL ENHANCERS **ON THE** SKIN **PERMEATION OF AMINOPYRINE**

, 1996

Abstract: The combined effect of 150 kHz ultrasound with 111 mW/cm(2) intensity and chemical **enhancers** on the **skin** permeation of aminopyrine (AMP) was investigated using excised hairless rat **skin** . Monoterpenes (L-menthol, L-calvone and D-limonene), laurocapram (Azone(R)), **glycerol** monocaprylate (Sefsol-318(R)), isopropyl myristate and **ethanol** were selected as **enhancers** . Combined application of ultrasound and **enhancers** **increased** the **skin** permeation rate (flux) of AMP compared with ultrasound or **enhancers** alone. **Better** effects were obtained by the combination with monoterpenes. The influence of detailed conditions of ultrasound and **enhancer** applications on the AMP flux was further investigated using L-menthol. The **enhancement** effect by this combination was **increased** with an **increase** in ultrasonic application duration and L-menthol concentration, suggesting that these conditions might be used...

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...Identifiers--HAIRLESS RAT; PENETRATION; **ETHANOL**; ABSORPTION; INVITRO
...Research Fronts: SONOCHEMICAL DESTRUCTION; CAVITATION BUBBLE; DILUTE AQUEOUS-SOLUTION; OSCILLATORY PRESSURE FIELD; TRANSIENT CAVITY)
94-1427 001 (**SKIN** PENETRATION **ENHANCERS** ; **IONTOPHORETIC**

TRANSDERMAL DELIVERY; FAPG BASE; PERCUTANEOUS PERMEATION; LUTEINIZING-HORMONE-RELEASING HORMONE (LHRH) IN-VITRO)

31/5,K/4 (Item 3 from file: 34)
DIALOG(R)File 34:SciSearch(R) Cited Ref Sci

04972071 Genuine Article#: UW198 Number of References: 38
Title: SYNERGISTIC EFFECTS OF CHEMICAL ENHANCERS AND THERAPEUTIC ULTRASOUND ON TRANSDERMAL DRUG-DELIVERY
Author(s): JOHNSON ME; MITRAGOTRI S; PATEL A; BLANKSCHTEIN D; LANGER R
Corporate Source: MIT,DEPT CHEM ENGN/CAMBRIDGE//MA/02139; MIT,DEPT CHEM ENGN/CAMBRIDGE//MA/02139
Journal: JOURNAL OF PHARMACEUTICAL SCIENCES, **1996** , V85, N7 (JUL), P 670-679
ISSN: 0022-3549
Language: ENGLISH Document Type: ARTICLE
Geographic Location: USA
Subfile: SciSearch; CC LIFE--Current Contents, Life Sciences
Journal Subject Category: CHEMISTRY; PHARMACOLOGY & PHARMACY
Abstract: The effects of (i) a series of chemical **enhancers** and (ii) the combination of these **enhancers** and therapeutic ultrasound (1 MHz, 1.4 W/cm(2), continuous) on transdermal drug transport are investigated. A series of chemical **enhancer** formulations, including (i) polyethylene glycol 200 dilaurate (PEG), (ii) isopropyl myristate (IM), (iii) **glycerol** trioleate (GT), (iv) **ethanol** /pH 7.4 phosphate buffered saline in a 1:1 ratio (50% EtOH), (v) 50% BOH saturated with linoleic acid (LA/EtOH), and (vi) phosphate buffered saline (PBS), as a control, are evaluated using corticosterone as a model drug, LA/EtOH is the most effective of these **enhancers** , **increasing** the corticosterone flux by 900-fold compared to that from PBS. Therapeutic ultrasound (1 MHz, 1.4 W/cm(2), continuous) **increases** the corticosterone **permeability** from all of the **enhancers** examined by up to 14-fold (LA/EtOH) and **increases** the corticosterone flux from the saturated solutions by up to 13000-fold (LA/EtOH), relative to that from PBS. Similar **enhancements** are obtained with LA/EtOH with and without ultrasound for four other model drugs, dexamethasone, estradiol, lidocaine, and testosterone. The **permeability enhancements** for all of these drugs resulting from the addition of linoleic acid to 50% EtOH **increase** with **increasing** drug molecular weight. Likewise, the **permeability enhancement** attained by ultrasound and LA/EtOH relative to passive EtOH exhibits a similar size dependence. A mechanistic explanation of this size dependence is provided. It is suggested that bilayer disordering agents, such as linoleic acid and ultrasound, transform the SC lipid bilayers into a fluid lipid bilayer phase or create a separate bulk oil phase. The difference in diffusivity of a given solute in SC bilayers and in either fluid bilayers or bulk oil is larger for larger solutes, thereby producing greater **enhancements** for larger solutes.
Identifiers--KeyWords Plus: HUMAN- **SKIN** INVITRO; OLEIC-ACID; PENETRATION **ENHANCERS** ; **STRATUM - CORNEUM** ; FATTY-ACIDS; **PERMEABILITY**; PERMEATION; ESTRADIOL; MEMBRANE; **ETHANOL**
Research Fronts: 94-1888 002 (PORCINE **STRATUM - CORNEUM** ; **SKIN PERMEABILITY** ; DERMAL ABSORPTION; TRANSDERMAL DELIVERY SYSTEMS; UNDERLYING TISSUE PHARMACOKINETICS; PERCUTANEOUS PERMEATION)
94-1427 001 (**SKIN** PENETRATION **ENHANCERS** ; **IONTOPHORETIC** TRANSDERMAL DELIVERY; FAPG BASE; PERCUTANEOUS PERMEATION; LUTEINIZING-HORMONE-RELEASING HORMONE (LHRH) IN-VITRO)
94-6319 001 (DERIVING STRUCTURE-ACTIVITY-RELATIONSHIPS; NONLINEAR MAP OF SUBSTITUENT CONSTANTS; MOLECULAR MODELING APPROACH; GEIPARVARIN

ANALOGS; ESCHERICHIA-COLI K-12)

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Title: SYNERGISTIC EFFECTS OF CHEMICAL ENHANCERS **AND THERAPEUTIC ULTRASOUND ON TRANSDERMAL DRUG-DELIVERY**

, 1996

Abstract: The effects of (i) a series of chemical **enhancers** and (ii) the combination of these **enhancers** and therapeutic ultrasound (1 MHz, 1.4 W/cm(2), continuous) on transdermal drug transport are investigated. A series of chemical **enhancer** formulations, including (i) polyethylene glycol 200 dilaurate (PEG), (ii) isopropyl myristate (IM), (iii) **glycerol** trioleate (GT), (iv) **ethanol** /pH 7.4 phosphate buffered saline in a 1:1 ratio (50% EtOH), (v) 50...

...evaluated using corticosterone as a model drug, LA/EtOH is the most effective of these **enhancers** , **increasing** the corticosterone flux by 900-fold compared to that from PBS. Therapeutic ultrasound (1 MHz, 1.4 W/cm(2), continuous) **increases** the corticosterone **permeability** from all of the **enhancers** examined by up to 14-fold (LA/EtOH) and **increases** the corticosterone flux from the saturated solutions by up to 13000-fold (LA/EtOH), relative to that from PBS. Similar **enhancements** are obtained with LA/EtOH with and without ultrasound for

four other model drugs, dexamethasone, estradiol, lidocaine, and testosterone. The **permeability enhancements** for all of these drugs resulting from the addition of linoleic acid to 50% EtOH **increase** with **increasing** drug molecular weight. Likewise, the **permeability enhancement** attained by ultrasound and LA/EtOH relative to passive EtOH exhibits a similar size dependence...

...in either fluid bilayers or bulk oil is larger for larger solutes, thereby producing greater **enhancements** for larger solutes.
...Identifiers--HUMAN- **SKIN** INVITRO; OLEIC-ACID; PENETRATION **ENHANCERS** ; **STRATUM - CORNEUM** ; FATTY-ACIDS; **PERMEABILITY**; PERMEATION; ESTRADIOL; MEMBRANE; **ETHANOL**
Research Fronts: 94-1888 002 (PORCINE **STRATUM - CORNEUM** ; **SKIN PERMEABILITY** ; DERMAL ABSORPTION; TRANSDERMAL DELIVERY SYSTEMS; UNDERLYING TISSUE PHARMACOKINETICS; PERCUTANEOUS PERMEATION)
94-1427 001 (**SKIN** PENETRATION **ENHANCERS** ; **IONTOPHORETIC** TRANSDERMAL DELIVERY; FAPG BASE; PERCUTANEOUS PERMEATION; LUTEINIZING-HORMONE-RELEASING HORMONE (LHRH) IN-VITRO)
94-6319...

31/5,K/5 (Item 4 from file: 34)
DIALOG(R)File 34:SciSearch(R) Cited Ref Sci

01246860 Genuine Article#: GH309 Number of References: 52
Title: EFFECTS OF ORGANIC-SOLVENT VEHICLES ON THE VIABILITY AND MORPHOLOGY OF ISOLATED PERFUSED PORCINE SKIN
Author(s): KING JR; MONTEIRORIVIERE NA
Corporate Source: N CAROLINA STATE UNIV,COLL VET MED,CTR CUTANEOUS PHARMACOL & TOXICOL,4700 HILLSBOROUGH ST/RALEIGH//NC/27606; N CAROLINA STATE UNIV,COLL VET MED,CTR CUTANEOUS PHARMACOL & TOXICOL,4700 HILLSBOROUGH ST/RALEIGH//NC/27606
Journal: TOXICOLOGY, **1991** , V69, N1, P11-26
Language: ENGLISH Document Type: ARTICLE
Geographic Location: USA
Subfile: SciSearch; CC LIFE--Current Contents, Life Sciences
Journal Subject Category: TOXICOLOGY; PHARMACOLOGY & PHARMACY
Abstract: Although many organic solvents are known to be cutaneous irritants, they are commonly utilized as vehicles in percutaneous absorption and toxicity studies. The isolated perfused porcine **skin** flap (IPPSF) is an alternative animal model that has been used to study percutaneous absorption and cutaneous toxicity. The purpose of this study was to evaluate the effect of five organic solvents (**ethanol** , acetone, **dimethyl sulfoxide** (**DMSO**), toluene, and cyclohexane) on biochemical viability parameters, vascular response, and epidermal morphology of the IPPSF. Cumulative **glucose** utilization (CGU), the ratio of lactate production/ **glucose** utilization (L/CGU ratio), and the leakage of lactate dehydrogenase (LDH) were used as biochemical indicators of alterations in **glucose** metabolism and flap viability. Only **ethanol** resulted in a statistically significant decrease in the average rate of CGU over the perfusion period. All of the solvent treatments resulted in slight **increases** in LDH release versus the controls. Vascular resistance (VR) was measured to examine the response of the cutaneous vasculature to these solvents, and most treatments resulted in a decreased VR in the terminal phases of perfusion. **Ethanol** was the only solvent to cause an apparent **increase** in terminal VR. **Light** microscopy demonstrated a moderate **increase** in intracellular edema in the **DMSO** , toluene, and acetone flaps. Ultrastructural evaluation showed focal blebbing of the nuclear

envelope and vesiculation of the rough endoplasmic reticulum in cells of the stratum basale and stratum spinosum layers with **DMSO** treatment. The IPPSF **allowed** the evaluation of subtle biochemical, vascular, and morphological changes associated with non-occlusive topical exposure to these organic solvents. These findings support the necessity of documenting vehicle effects which might mask or otherwise alter sublte, but potentially important, compound-specific responses.

Descriptors--Author Keywords: SOLVENT; VEHICLE; **SKIN** FLAP; VIABILITY; HISTOPATHOLOGY; ULTRASTRUCTURE

Identifiers--KeyWords Plus: LASER DOPPLER FLOWMETRY; PERCUTANEOUS-ABSORPTION; LIDOCAINE **IONTOPHORESIS** ; PHARMACOKINETIC MODEL; INDUSTRIAL SOLVENTS; FLAP; PENETRATION; INVITRO; **PERMEABILITY**; DEFINITION

Research Fronts: 89-0541 004 (**SKIN** **PERMEABILITY** ; INVITRO PERCUTANEOUS PENETRATION; TRANS-EPIDERMAL WATER-LOSS; TRANSDERMAL DELIVERY OF LEVONORGESTREL; **STRATUM** - **CORNEUM** LIPIDS)

89-2190 001 (PHARMACOKINETICS OF ALFENTANIL; TRANSDERMAL FENTANYL; SUFENTANIL ANESTHESIA; 1-DODECYLAZACYCLOHEPTAN-2-ONE (AZONE); **SKIN** PERMEATION; WATER-SOLUBLE DRUGS)

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Title: EFFECTS OF ORGANIC-SOLVENT VEHICLES ON THE VIABILITY AND MORPHOLOGY OF ISOLATED PERFUSED PORCINE SKIN
, **1991**

...Abstract: are commonly utilized as vehicles in percutaneous absorption and toxicity studies. The isolated perfused porcine **skin** flap (IPPSF) is an alternative animal model that has been used to study percutaneous absorption...

...toxicity. The purpose of this study was to evaluate the effect of five organic solvents (**ethanol** , acetone, **dimethyl sulfoxide** (**DMSO**), toluene, and cyclohexane) on biochemical viability parameters, vascular response, and epidermal morphology of the IPPSF. Cumulative **glucose** utilization (CGU), the ratio of lactate production/ **glucose** utilization (L/CGU ratio), and the leakage of lactate dehydrogenase (LDH) were used as biochemical indicators of alterations in **glucose** metabolism and flap viability. Only **ethanol** resulted in a statistically significant decrease in the average rate of CGU over the perfusion period. All of the solvent treatments resulted in slight **increases** in LDH release versus the controls. Vascular resistance (VR) was measured to examine the response...

...solvents, and most treatments resulted in a decreased VR in the terminal phases of perfusion. **Ethanol** was the only solvent to cause an apparent **increase** in terminal VR. **Light** microscopy demonstrated a moderate **increase** in intracellular edema in the **DMSO** , toluene, and acetone flaps. Ultrastructural evaluation showed focal blebbing of the nuclear envelope and vesiculation...

...the rough endoplasmic reticulum in cells of the stratum basale and stratum spinosum layers with **DMSO** treatment. The IPPSF **allowed** the evaluation of subtle biochemical, vascular, and morphological changes associated with non-occlusive topical exposure...

...Identifiers--LASER DOPPLER FLOWMETRY; PERCUTANEOUS-ABSORPTION; LIDOCAINE **IONTOPHORESIS** ; PHARMACOKINETIC MODEL; INDUSTRIAL SOLVENTS; FLAP; PENETRATION; INVITRO; **PERMEABILITY**; DEFINITION

Research Fronts: 89-0541 004 (**SKIN PERMEABILITY** ; INVITRO PERCUTANEOUS PENETRATION; TRANS-EPIDERMAL WATER-LOSS; TRANSDERMAL DELIVERY OF LEVONORGESTREL; **STRATUM - CORNEUM** LIPIDS)

89-2190 001 (PHARMACOKINETICS OF ALFENTANIL; TRANSDERMAL FENTANYL; SUFENTANIL ANESTHESIA; 1-DODECYLAZACYCLOHEPTAN-2-ONE (AZONE); **SKIN** PERMEATION; WATER-SOLUBLE DRUGS)

31/5,K/6 (Item 5 from file: 34)
DIALOG(R)File 34:SciSearch(R) Cited Ref Sci

01011865 Genuine Article#: FN212 Number of References: 33

Title: SERUM GLUCOSE **AND INSULIN RESPONSES TO AN INSULIN-CONTAINING OPHTHALMIC SOLUTION ADMINISTERED TOPICALLY IN CLINICALLY NORMAL CATS**

Author(s): HOPPER PE; MURPHY CJ; FELDMAN EC; NELSON RW; BOTTOMS GD; FRANTI CE

Corporate Source: ENCINA VET HOSP,2803 YGNACIO VALLEY RD/WALNUT CREEK//CA/94598; UNIV CALIF DAVIS,VET MED TEACHING HOSP,SMALL ANIM INTERNAL MED SERV/DAVIS//CA/95616; UNIV CALIF DAVIS,VET MED TEACHING HOSP,OPHTHALMOL SERV/DAVIS//CA/95616; UNIV CALIF DAVIS,SCH VET MED,DEPT REPROD/DAVIS//CA/95616; UNIV CALIF DAVIS,SCH VET MED,DEPT EPIDEMIOL & PREVENT MED/DAVIS//CA/95616; PURDUE UNIV,SCH VET MED,DEPT VET PHYSIOL & PHARMACOL/W LAFAYETTE//IN/47907; PURDUE UNIV,SCH VET MED,DEPT VET CLIN SCI/W LAFAYETTE//IN/47907

Journal: AMERICAN JOURNAL OF VETERINARY RESEARCH, **1991** , V52, N6, P903-907

Language: ENGLISH Document Type: ARTICLE

Geographic Location: USA

Subfile: SciSearch; CC AGRI--Current Contents, Agriculture, Biology & Environmental Sciences

Journal Subject Category: VETERINARY MEDICINE

Abstract: Serum **glucose** and immunoreactive insulin concentrations were monitored after topical administration of an insulin-containing ophthalmic solution in 20 clinically normal cats. Three ophthalmic surface-acting agents, benzalkonium chloride, **dimethyl sulfoxide** , and proparacaine hydrochloride, were evaluated individually for their effectiveness in **enhancing** absorption of topically applied insulin. The ophthalmic effects of insulin-containing ophthalmic preparations were assessed by complete ophthalmic examination before and at the conclusion of each test period. Withholding of food overnight (12 hours) preceded each topical application of insulin-containing ophthalmic solution (12.25 to 26.4 U/cat), either alone or in combination with surface-acting agents, after which blood samples were drawn serially from an indwelling IV catheter over a period of 8 hours. Baseline serum insulin concentration, after food was withheld for 12 hours, in nonstressed cats was 6.0-mu-U/ml (geometric mean), and an exponentiation of the logarithmic quantity (mean +/- SD) yielded values of 1.5 to 23.0-mu-U/ml. All ophthalmic solutions tested failed to significantly lower serum **glucose** concentration or **increase** serum insulin concentration. Solutions used did not induce deleterious effect on ocular structures. Results indicate that topical administration of insulin-containing ophthalmic solution, either alone at the concentrations used or in combination with surface-acting agents, did not result in effective absorption of insulin across the **conjunctival** and lacrimal nasal mucosa in biologically relevent quantities. Thus, this route of insulin administration, under these specific conditions, is not an effective alternative or adjunct to SC administration of insulin for treatment of cats with insulin-dependent diabetes mellitus or severe noninsulin-dependent diabetes mellitus.

Identifiers--KeyWords Plus: BENZALKONIUM CHLORIDE; CORNEAL **EPITHELIUM** ; DIABETIC SUBJECTS; **PERMEABILITY**; EYES

Research Fronts: 89-1722 001 (TRANSDERMAL **IONTOPHORETIC** DRUG DELIVERY; NASAL ABSORPTION OF INSULIN; FACTORS AFFECTING SULFISOXAZOLE TRANSPORT)
89-5694 001 (CORNEAL **EPITHELIUM** ; BENZALKONIUM CHLORIDE; TOXIC ULCERATIVE KERATOPATHY)

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WOOST PG, 1985, V40, P47, EXP EYE RES
YOSHIMITUS Y, 1981, V4, P454, DIABETES CARE

Title: SERUM GLUCOSE **AND INSULIN RESPONSES TO AN INSULIN-CONTAINING OPHTHALMIC SOLUTION ADMINISTERED TOPICALLY IN CLINICALLY NORMAL CATS , 1991**

Abstract: Serum **glucose** and immunoreactive insulin concentrations were monitored after topical administration of an insulin-containing ophthalmic solution in 20 clinically normal cats. Three ophthalmic surface-acting agents, benzalkonium chloride, **dimethyl sulfoxide** , and proparacaine hydrochloride, were evaluated individually for their effectiveness in **enhancing** absorption of topically applied insulin. The ophthalmic effects of insulin-containing ophthalmic preparations were assessed...

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...Identifiers--BENZALKONIUM CHLORIDE; CORNEAL **EPITHELIUM** ; DIABETIC SUBJECTS; **PERMEABILITY**; EYES

Research Fronts: 89-1722 001 (TRANSDERMAL **IONTOPHORETIC** DRUG DELIVERY; NASAL ABSORPTION OF INSULIN; FACTORS AFFECTING SULFISOXAZOLE TRANSPORT)
89-5694 001 (CORNEAL **EPITHELIUM** ; BENZALKONIUM CHLORIDE; TOXIC ULCERATIVE KERATOPATHY)

31/5,K/7 (Item 1 from file: 73)
DIALOG(R)File 73:EMBASE

06986820 EMBASE No: 1997272901

Iontophoretic **transdermal absorption of insulin and calcitonin in rats with newly-devised switching technique and addition of urea**

Tomohira Y.; Machida Y.; Onishi H.; Nagai T.
Y. Machida, Department of Clinical Pharmacy, Hoshi University, Ebara 2-4-41, Shinagawa-ku, Tokyo 142 Japan

International Journal of Pharmaceutics (INT. J. PHARM.) (Netherlands) 1997, 155/2 (231-239)
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DOCUMENT TYPE: Journal; Article
LANGUAGE: ENGLISH SUMMARY LANGUAGE: ENGLISH
NUMBER OF REFERENCES: 9

The effect of urea and reversing polarity of electrodes (switching technique) in **iontophoresis** was investigated in order to get a **better** transdermal absorption of peptide drugs, insulin and calcitonin, and to reduce dermal irritation caused by the **iontophoresis** . Two cells with an electrode were set on the hair-removed abdominal **skin** of diabetic or oophorectomized rats. After putting peptide solution into the anode side or both of the cells, an electric current with pulsed rectangular wave form (4 kHz, 50% duty) was passed through the **skin** for 2 h at 0.075 mA cmsup -sup 2 (insulin) and for 50 min or 2 h at 0.015 mA cmsup -sup 2 (calcitonin). Absorption of insulin and calcitonin was estimated from the reduction of **glucose** and calcium levels in the plasma of the rats, respectively. When the polarity of electrodes was reversed at intervals of 20 min for insulin and 25 min for calcitonin, absorption of the drug was effectively **enhanced** . The addition of urea to the insulin solution together with the switching technique brought about a remarkably facilitated absorption of insulin. Moreover, comparison of the **skin** conditions between switching and non-switching experiments suggested that irritation of **skin** could be reduced by employment of the switching **iontophoresis** .

MANUFACTURER NAMES: sigma
DRUG DESCRIPTORS:
*calcitonin--drug interaction--it; *calcitonin--pharmacokinetics--pk; *insulin--drug interaction--it; *insulin--pharmacokinetics--pk; *urea--drug interaction--it
penetration **enhancing** **agent**
MEDICAL DESCRIPTORS:
* **skin** absorption
animal cell; animal tissue; article; biological model; controlled study; depolarization; drug absorption; female; **iontophoresis** ; male; nonhuman; priority journal; rat; **skin** irritation; transdermal drug administration
CAS REGISTRY NO.: 12321-44-7, 21215-62-3, 9007-12-9 (calcitonin); 9004-10-8 (insulin); 57-13-6 (urea)
SECTION HEADINGS:
030 Clinical and Experimental Pharmacology
037 Drug Literature Index
039 Pharmacy

Iontophoretic **transdermal absorption of insulin and calcitonin in rats with newly-devised switching technique and addition...**

The effect of urea and reversing polarity of electrodes (switching technique) in **iontophoresis** was investigated in order to get a **better** transdermal absorption of peptide drugs, insulin and calcitonin, and to reduce dermal irritation caused by the **iontophoresis** . Two cells with an electrode were set on the hair-removed abdominal **skin** of diabetic or oophorectomized rats. After putting peptide solution into the anode side or both...

...electric current with pulsed rectangular wave form (4 kHz, 50% duty) was passed through the **skin** for 2 h at 0.075 mA cmsup -sup 2 (insulin) and for 50 min...

...cmsup -sup 2 (calcitonin). Absorption of insulin and calcitonin was estimated from the reduction of **glucose** and calcium levels in the plasma of the rats, respectively. When the polarity of electrodes...

...20 min for insulin and 25 min for calcitonin, absorption of the drug was effectively **enhanced** . The addition of urea to the insulin solution together with the switching technique brought about a remarkably facilitated absorption of insulin. Moreover, comparison of the **skin** conditions between switching and non-switching experiments suggested that irritation of **skin** could be reduced by employment of the switching **iontophoresis** .
DRUG DESCRIPTORS:
penetration **enhancing** **agent**
MEDICAL DESCRIPTORS:
* **skin** absorption
animal cell; animal tissue; article; biological model; controlled study; depolarization; drug absorption; female; **iontophoresis** ; male; nonhuman; priority journal; rat; **skin** irritation; transdermal drug administration
1997

31/5,K/8 **(Item 2 from file: 73)**
DIALOG(R)File 73:EMBASE

06742844 EMBASE No: 1997024317
Current status and future prospects of transdermal drug delivery
Guy R.H.
R.H. Guy, Ctr. Interuniv Recherche d'Enseignem, Campus Universitaire, Parc d'Affaires International, F-74166 Archamps France
AUTHOR EMAIL: guy@sc2a.unige.ch
Pharmaceutical Research (PHARM. RES.) (United States) 1996, 13/12 (1765-1769)
CODEN: PHREE ISSN: 0724-8741
DOCUMENT TYPE: Journal; Review
LANGUAGE: ENGLISH
NUMBER OF REFERENCES: 35
DRUG DESCRIPTORS:
clonidine; erythropoietin; estradiol; fentanyl; gamma interferon; **glyceryl** trinitrate; lidocaine--pharmacokinetics--pk; nicotine; penetration **enhancing** **agent** ; scopolamine; testosterone
MEDICAL DESCRIPTORS:
* **skin** penetration; *transdermal drug administration
controlled drug release; drug delivery system; human; **iontophoresis** ; nonhuman; priority journal; review; **stratum** **corneum** ; technology; ultrasound
CAS REGISTRY NO.: 4205-90-7, 4205-91-8, 57066-25-8 (clonidine); 11096-26-7 (erythropoietin); 50-28-2 (estradiol); 437-38-7 (fentanyl); 82115-62-6 (gamma interferon); 55-63-0 (**glyceryl** trinitrate); 137-58-6, 24847-67-4, 56934-02-2, 73-78-9 (lidocaine); 54-11-5 (nicotine); 138-12-5, 51-34-3, 55-16-3 (scopolamine); 58-22-0 (testosterone
SECTION HEADINGS:
030 Clinical and Experimental Pharmacology
037 Drug Literature Index
039 Pharmacy

DRUG DESCRIPTORS:
clonidine; erythropoietin; estradiol; fentanyl; gamma interferon; **glyceryl** trinitrate; lidocaine--pharmacokinetics--pk; nicotine; penetration **enhancing agent** ; scopolamine; testosterone
MEDICAL DESCRIPTORS:
* **skin** penetration; *transdermal drug administration
controlled drug release; drug delivery system; human; **iontophoresis** ; nonhuman; priority journal; review; **stratum corneum** ; technology; ultrasound
...CAS REGISTRY NO.: 28-2 (estradiol); 437-38-7 (fentanyl); 82115-62-6 (gamma interferon); 55-63-0 (**glyceryl** trinitrate); 137-58-6...
1996

31/5,K/9 (Item 3 from file: 73)
DIALOG(R)File 73:EMBASE

06490578 EMBASE No: 1996135448
Drug penetration into human skin **and their modulation**
WIRKSTOFFPENETRATION IN DIE HAUT UND DEREN MODULATION
Neubert R.; Schmalfuss U.; Wohlrab W.; Huschka C.
Fachbereich Pharmazie, Martin-Luther-Universitat,
Wolfgang-Langenbeck-Strasse 4,06120 Halle Germany
Pharmazeutische Zeitung (PHARM. ZTG.) (Germany) 1996, 141/17 (11-16+18+21-23)
CODEN: PZSED ISSN: 0031-7136
DOCUMENT TYPE: Journal; Short Survey
LANGUAGE: GERMAN SUMMARY LANGUAGE: GERMAN
BRAND NAME/MANUFACTURER NAME: azone
DRUG DESCRIPTORS:
*analgesic agent--pharmacokinetics--pk; *analgesic agent--pharmaceutics--pr ; *anesthetic agent--pharmacokinetics--pk; *anesthetic agent--pharmaceutics --pr; *antihistaminic agent--pharmaceutics--pr; *antihistaminic agent --pharmacokinetics--pk; *antiinfective agent--pharmacokinetics--pk; * antiinfective agent--pharmaceutics--pr; *antineoplastic agent --pharmacokinetics--pk; *antineoplastic agent--pharmaceutics--pr; * antivirus agent--pharmaceutics--pr; *antivirus agent--pharmacokinetics--pk; *corticosteroid--pharmaceutics--pr; *corticosteroid--pharmacokinetics--pk; *nonsteroid antiinflammatory agent--pharmacokinetics--pk; *nonsteroid antiinflammatory agent--pharmaceutics--pr; *penetration **enhancing agent** 2 pyrrolidinone--pharmaceutics--pr; 2 pyrrolidone derivative--pharmaceutics --pr; alcohol derivative--pharmaceutics--pr; cyclodextrin derivative --pharmaceutics--pr; decyl methyl sulfoxide--pharmaceutics--pr; **dimethyl sulfoxide** --pharmaceutics--pr; drug vehicle; fatty acid derivative --pharmaceutics--pr; **glycerol** --pharmaceutics--pr; laurocapram --pharmaceutics--pr; liposome--pharmaceutics--pr; prodrug--pharmaceutics --pr; propylene glycol--pharmaceutics--pr; terpene derivative --pharmaceutics--pr; unindexed drug; urea--pharmaceutics--pr
MEDICAL DESCRIPTORS:
* **skin** absorption; * **skin** penetration
drug formulation; drug penetration; drug release; human; **iontophoresis** ; short survey; solubilization; **stratum corneum** ; topical drug administration; transdermal drug administration; drug dosage form; emulsion ; hydrogel
CAS REGISTRY NO.: 616-45-5 (2 pyrrolidinone); 3079-28-5 (decyl methyl sulfoxide); **67-68-5** (**dimethyl sulfoxide**); 56-81-5 (**glycerol**); 59227-89-3 (laurocapram); 57-55-6 (propylene glycol); 57-13-6 (urea)
SECTION HEADINGS:

013 Dermatology and Venereology
030 Clinical and Experimental Pharmacology
037 Drug Literature Index

Drug penetration into human skin **and their modulation**
DRUG DESCRIPTORS:
...*pr; *corticosteroid--pharmacokinetics--pk; *nonsteroid antiinflammatory agent--pharmacokinetics--pk; *nonsteroid antiinflammatory agent --pharmaceutics--pr; *penetration **enhancing agent** ...pharmaceutics--pr; alcohol derivative--pharmaceutics--pr; cyclodextrin derivative--pharmaceutics--pr; decyl methyl sulfoxide--pharmaceutics--pr; **dimethyl sulfoxide** --pharmaceutics--pr; drug vehicle; fatty acid derivative--pharmaceutics--pr; **glycerol** --pharmaceutics--pr; laurocapram --pharmaceutics--pr; liposome--pharmaceutics--pr; prodrug--pharmaceutics --pr; propylene glycol--pharmaceutics--pr...
MEDICAL DESCRIPTORS:
* **skin** absorption; * **skin** penetration
drug formulation; drug penetration; drug release; human; **iontophoresis** ; short survey; solubilization; **stratum corneum** ; topical drug administration; transdermal drug administration; drug dosage form; emulsion ; hydrogel
CAS REGISTRY NO.: 616-45-5 (2 pyrrolidinone); 3079-28-5 (decyl methyl sulfoxide); **67-68-5** (**dimethyl sulfoxide**); 56-81-5 (**glycerol**); 59227-89-3 (laurocapram); 57-55-6 (propylene glycol); 57-13-6 (urea)
1996

31/5,K/10 (Item 4 from file: 73)
DIALOG(R)File 73:EMBASE

05697625 EMBASE No: 1994103998
Polymers for transdermal drug delivery systems
Sugibayashi K.; Morimoto Y.
Faculty of Pharmaceutical Sciences, Josai University, 1-1 Keyakidai,Sakado, Saitama 350-02 Japan
Journal of Controlled Release (J. CONTROL. RELEASE) (Netherlands) 1994 , 29/1-2 (177-185)
CODEN: JCREE ISSN: 0168-3659
DOCUMENT TYPE: Journal; Conference Paper
LANGUAGE: ENGLISH SUMMARY LANGUAGE: ENGLISH

Advances in transdermal delivery systems (TDS) and the technology involved have been rapid because of the sophistication of polymer science which now **allows** incorporation of polymeric additives in TDS in adequate quantity. Polymer selection and design are of prime importance in formulating various criteria of new TDS. In this review paper, typical polymers in topical drug formulations are introduced by category, and their usefulness is discussed. Several methods for regulation of release and **skin** permeation of drug by polymers are also introduced and evaluated.

BRAND NAME/MANUFACTURER NAME: nitrodisc/searle; transderm scop/alza corporation; transderm nitro/alza corporation; nitriderm tts/alza corporation; nitroderm tts/alza corporation; nitrodur/key pharmaceuticals; diafusor/key pharmaceuticals; deponit/lohmann; minitran/riker 3m; nitrocine /hercon; nitrol/paco; frandol tape/toa eiyo
MANUFACTURER NAMES: searle; alza corporation; key pharmaceuticals; lohmann; riker 3m; hercon; paco; toa eiyo
DRUG DESCRIPTORS:
*polymer--pharmaceutics--pr

alginic acid--pharmaceutics--pr; casein--pharmaceutics--pr; clonidine --pharmaceutics--pr; **glyceryl** trinitrate--pharmaceutics--pr; fentanyl --pharmaceutics--pr; gelatin--pharmaceutics--pr; gum arabic--pharmaceutics --pr; gum tragacanth--pharmaceutics--pr; isosorbide dinitrate --pharmaceutics--pr; mepindolol--pharmaceutics--pr; paraffin--pharmaceutics --pr; penetration **enhancing** **agent** --pharmaceutics--pr; polyethylene --pharmaceutics--pr; polysiloxane--pharmaceutics--pr; polystyrene --pharmaceutics--pr; polyurethan--pharmaceutics--pr; polyvinyl acetate --pharmaceutics--pr; polyvinyl alcohol--pharmaceutics--pr; scopolamine --pharmaceutics--pr; starch--pharmaceutics--pr; unindexed drug; unclassified drug
MEDICAL DESCRIPTORS:
*polymerization; * **skin** **permeability** ; *drug delivery system conference paper; device; drug formulation; human; **iontophoresis** ; nonhuman; physical chemistry; priority journal; reservoir; technology; topical drug administration; transdermal drug administration; pharmaceutics ; ointment
DRUG TERMS (UNCONTROLLED): bioadhesive agent--pharmaceutics--pr; frandol tape; polybutadiene--pharmaceutics--pr; polyisoprene--pharmaceutics--pr
CAS REGISTRY NO.: 28961-37-7, 29894-36-8, 9005-32-7, 9005-38-3 (alginic acid); 9000-71-9 (casein); 4205-90-7, 4205-91-8, 57066-25-8 (clonidine) ; 55-63-0 (**glyceryl** trinitrate); 437-38-7 (fentanyl); 9000-70-8 (gelatin); 9000-01-5 (gum arabic); 9000-65-1 (gum tragacanth); 87-33-2 (isosorbide dinitrate); 23694-81-7, 56396-94-2 (mepindolol); 9003-17-2 (polybutadiene); 9002-88-4 (polyethylene); 9003-31-0 (polyisoprene); 9003-53-6 (polystyrene); 61789-63-7 (polyurethan); 9003-20-7 (polyvinyl acetate); 37380-95-3, 9002-89-5 (polyvinyl alcohol); 138-12-5, 51-34-3, 55-16-3 (scopolamine); 9005-25-8, 9005-84-9 (starch
SECTION HEADINGS:
013 Dermatology and Venereology
027 Biophysics, Bioengineering and Medical Instrumentation
030 Clinical and Experimental Pharmacology
037 Drug Literature Index

...the technology involved have been rapid because of the sophistication of polymer science which now **allows** incorporation of polymeric additives in TDS in adequate quantity. Polymer selection and design are of...

...introduced by category, and their usefulness is discussed. Several methods for regulation of release and **skin** permeation of drug by polymers are also introduced and evaluated.
DRUG DESCRIPTORS:
alginic acid--pharmaceutics--pr; casein--pharmaceutics--pr; clonidine --pharmaceutics--pr; **glyceryl** trinitrate--pharmaceutics--pr; fentanyl --pharmaceutics--pr; gelatin--pharmaceutics--pr; gum arabic--pharmaceutics --pr; gum tragacanth--pharmaceutics--pr; isosorbide dinitrate --pharmaceutics--pr; mepindolol--pharmaceutics--pr; paraffin--pharmaceutics --pr; penetration **enhancing** **agent** --pharmaceutics--pr; polyethylene --pharmaceutics--pr; polysiloxane--pharmaceutics--pr; polystyrene --pharmaceutics--pr; polyurethan--pharmaceutics--pr; polyvinyl...
MEDICAL DESCRIPTORS:
*polymerization; * **skin** **permeability** ; *drug delivery system conference paper; device; drug formulation; human; **iontophoresis** ; nonhuman; physical chemistry; priority journal; reservoir; technology; topical drug administration; transdermal drug administration; pharmaceutics ; ointment
...CAS REGISTRY NO.: 57066-25-8 (clonidine); 55-63-0 (**glyceryl** trinitrate); 437-38-7 (fentanyl); 9000-70-8 (gelatin); 9000-01-5 (gum arabic); 9000...
1994

31/5,K/11 (Item 5 from file: 73)
DIALOG(R)File 73:EMBASE

05385821 EMBASE No: 1993153920
Transdermal penetration enhancers : **Categorisation**
Soni S.; Dixit V.K.
Dept. of Pharmaceutical Sciences,Sagar 470 003 India
Indian Drugs (INDIAN DRUGS) (India) 1992, 29/11 (465-472)
CODEN: INDRB ISSN: 0019-462X
DOCUMENT TYPE: Journal; Review
LANGUAGE: ENGLISH SUMMARY LANGUAGE: ENGLISH
DRUG DESCRIPTORS:
*penetration **enhancing agent** --drug comparison--cm; *penetration **enhancing agent** --pharmacology--pd
alkanol; cineole; cyclopeptide; **dimethyl sulfoxide** ; dodecyl sulfate sodium; fatty acid; **glycerol** ; limonene; macrogol; macrogol stearate; pyrrolidine derivative; solvent; surfactant; terpene; urea derivative; unclassified drug
MEDICAL DESCRIPTORS:
* **skin permeability**
bioavailability; drug targeting; **iontophoresis** ; review; structure activity relation; transdermal drug administration; ultrasound
DRUG TERMS (UNCONTROLLED): lauryl ether; thioglycolate calcium
CAS REGISTRY NO.: 470-82-6, 55962-72-6 (cineole); **67-68-5** (**dimethyl sulfoxide**); 151-21-3 (dodecyl sulfate sodium); 56-81-5 (**glycerol**); 138-86-3, 5989-27-5 (limonene); 25322-68-3 (macrogol); 9004-99-3 (macrogol stearate); 814-71-1 (thioglycolate calcium
SECTION HEADINGS:
013 Dermatology and Venereology
030 Clinical and Experimental Pharmacology
037 Drug Literature Index

Transdermal penetration enhancers : **Categorisation**
DRUG DESCRIPTORS:
*penetration **enhancing agent** --drug comparison--cm; *penetration **enhancing agent** --pharmacology--pd
alkanol; cineole; cyclopeptide; **dimethyl sulfoxide** ; dodecyl sulfate sodium; fatty acid; **glycerol** ; limonene; macrogol; macrogol stearate; pyrrolidine derivative; solvent; surfactant; terpene; urea derivative; unclassified drug
MEDICAL DESCRIPTORS:
* **skin permeability**
bioavailability; drug targeting; **iontophoresis** ; review; structure activity relation; transdermal drug administration; ultrasound
...CAS REGISTRY NO.: 55962-72-6 (cineole); **67-68-5** (**dimethyl sulfoxide**); 151-21-3 (dodecyl sulfate sodium); 56-81-5 (**glycerol**); 138-86-3...
1992

31/5,K/12 (Item 1 from file: 144)
DIALOG(R)File 144:Pascal

14125673 PASCAL No.: 99-0321778
Coherent and non-coherent light **transport in living tissues impregnated by endogenous or exogenous fluids and gels**
Photon propagation in tissues IV : Stockholm, 9-11 September 1998

TUCHIN V V
BENARON David A, ed; CHANCE Britton, ed; FERRARI Marco, ed; KOHL Matthias , ed
Saratov State University, Astrakhanskaya 83, Saratov 410026, Russia
International Society for Optical Engineering, Bellingham WA, United States.
Photon propagation in tissues. Conference, 4 (Stockholm SWE) 1998-09-09
Journal: SPIE proceedings series, **1998** , 3566 161-175
ISBN: 0-8194-3028-5 ISSN: 1017-2653 Availability: INIST-21760; 354000084601570190
No. of Refs.: 44 ref.
Document Type: P (Serial); C (Conference Proceedings) ; A (Analytic)
Country of Publication: United States
Language: English
Results on the human **sclera** and **skin** **optical** properties controlled by employing **administration** of various **chemical** agents are presented. CW transmittance and reflectance measurements as well as intensity correlation experiments were used for tissue structural and **optical** properties monitoring. As chemical applicators - controllers osmotically active solutions, such as trazograph, **glucose** , polyethylene glycol (PEG), propylene glycol (PPG), **glycerol** , as well as aprotonic solutions like dimethyl sulphoxide (**DMSO**) were used. The characteristic time response of the human **sclera** **optical** clearing lying in the range 3-10 min was defined. The diffusion coefficients describing the samples of the human **sclera** **permeability** to various solutes were experimentally estimated. Presented results are general and can be applicable for description of many other fibrous tissues.

English Descriptors: Wave propagation; **Optical** properties; Tissue; **Sclera** ; Derm; Chemical product; Structural analysis; Time response; **Light** scattering; Human; Spectrophotometry; In vitro; In vivo

French Descriptors: Propagation onde; Propriete optique; Tissu; Sclerotique ; Derme; Produit chimique; Analyse structurale; Reponse temporelle; Diffusion lumiere; Homme; Spectrophotometrie; In vitro; In vivo

Classification Codes: 002A08F01

Coherent and non-coherent light **transport in living tissues impregnated by endogenous or exogenous fluids and gels**
1998

Results on the human **sclera** and **skin** **optical** properties controlled by employing **administration** of various **chemical** agents are presented. CW transmittance and reflectance measurements as well as intensity correlation experiments were used for tissue structural and **optical** properties monitoring. As chemical applicators - controllers osmotically active solutions, such as trazograph, **glucose** , polyethylene glycol (PEG), propylene glycol (PPG), **glycerol** , as well as aprotonic solutions like dimethyl sulphoxide (**DMSO**) were used. The characteristic time response of the human **sclera** **optical** clearing lying in the range 3-10 min was defined. The diffusion coefficients describing the samples of the human **sclera** **permeability** to various solutes were experimentally estimated. Presented results are general and can be applicable for...

English Descriptors: Wave propagation; **Optical** properties; Tissue; **Sclera** ; Derm; Chemical product; Structural analysis; Time response; **Light** scattering; Human; Spectrophotometry; In vitro; In vivo

31/5,K/13 (Item 1 from file: 155)
DIALOG(R)File 155:MEDLINE(R)

10230024 96031326 PMID: 7550099

Combined effect of d-limonene pretreatment and temperature on the rat skin permeation of lipophilic and hydrophilic drugs.

Ohara N; Takayama K; Nagai T
Department of Pharmaceutics, Hoshi University, Tokyo, Japan.

Biological & pharmaceutical bulletin (JAPAN) Mar **1995** , 18 (3) p439-42, ISSN 0918-6158 Journal Code: 9311984
Document type: Journal Article
Languages: ENGLISH
Main Citation Owner: NLM
Record type: Completed
Subfile: INDEX MEDICUS

The combined effect of d-limonene and temperature on the **skin** permeation of lipophilic and hydrophilic penetrants has been investigated in rats in vitro. Prednisolone was used as a lipophilic penetrant, and **glucose** and isoniazid were used as hydrophilic ones, respectively. When the **skin** was pretreated with 30% **ethanol** without d-limonene, the steady state **permeability** coefficient (P) of every penetrant through the **skin** was difficult to calculate because of very low **permeability** . On the other hand, the cumulative amount of each penetrant **increased** with an **increase** in temperature when the **skin** was pretreated with 1.5% d-limonene in 30% **ethanol** . The Arrhenius plots of P values for **glucose** and isoniazid showed a linear relationship, and the activation energies of **skin** permeation were estimated to be 87.6 and 66.5 kJ/mol, respectively. When prednisolone was used as penetrant, however, the Arrhenius plot of P values exhibited a convex curvature. This may suggest that the combined use of d-limonene and temperature effectively changes the barrier structure of the non-polar pathway in the **stratum** corneum , while no synergistic effect was observed on the polar pathway.

Tags: Animal; In Vitro; Male; Support, Non-U.S. Gov't
Descriptors: Antineoplastic Agents, Phytogenic--pharmacology--PD; *Prednisolone--pharmacokinetics--PK; * **Skin** --metabolism--ME; * **Skin** Absorption--drug effects--DE; * **Skin** Absorption--physiology--PH; *Terpenes--pharmacology--PD; **Administration** , Cutaneous; Chemistry, **Physical** ; **Glucose** --chemistry--CH; **Glucose** --pharmacokinetics--PK; Isoniazid--chemistry--CH; Isoniazid--pharmacokinetics--PK; Prednisolone --chemistry--CH; Rats; Rats, Wistar; **Skin** --drug effects--DE; Solubility; Temperature
CAS Registry No.: 0 (Antineoplastic Agents, Phytogenic); 0 (Terpenes) ; 138-86-3 (limonene); 50-24-8 (Prednisolone); **50-99-7 (Glucose)** ; 54-85-3 (Isoniazid)
Record Date Created: 19951106
Record Date Completed: 19951106

Combined effect of d-limonene pretreatment and temperature on the rat skin permeation of lipophilic and hydrophilic drugs.

Mar **1995** ,

The combined effect of d-limonene and temperature on the **skin** permeation of lipophilic and hydrophilic penetrants has been investigated in rats in vitro. Prednisolone was used as a lipophilic penetrant, and **glucose** and isoniazid were used as hydrophilic ones, respectively. When the **skin** was pretreated with 30% **ethanol** without d-limonene, the steady state **permeability** coefficient (P) of every penetrant through the **skin** was difficult to calculate because of very low **permeability** . On the other hand, the cumulative amount of each penetrant **increased** with an **increase** in temperature when the **skin** was pretreated with 1.5%

d-limonene in 30% **ethanol** . The Arrhenius plots of P values for **glucose** and isoniazid showed a linear relationship, and the activation energies of **skin** permeation were estimated to be 87.6 and 66.5 kJ/mol, respectively. When prednisolone...

... limonene and temperature effectively changes the barrier structure of the non-polar pathway in the **stratum corneum** , while no synergistic effect was observed on the polar pathway.

Descriptors: Antineoplastic Agents, Phytogenic--pharmacology--PD; *Prednisolone--pharmacokinetics--PK; * **Skin** --metabolism--ME; * **Skin** Absorption--drug effects--DE; * **Skin** Absorption--physiology--PH; *Terpenes--pharmacology--PD; **Administration** , Cutaneous; Chemistry, **Physical** ; **Glucose** --chemistry--CH; **Glucose** --pharmacokinetics--PK; Isoniazid--chemistry--CH; Isoniazid--pharmacokinetics--PK; Prednisolone --chemistry--CH; Rats; Rats, Wistar; **Skin** --drug effects--DE; Solubility; Temperature

CAS Registry No.: 0 (Antineoplastic Agents, Phytogenic); 0 (Terpenes) ; 138-86-3 (limonene); 50-24-8 (Prednisolone); **50-99-7 (Glucose)** ; 54-85-3 (Isoniazid)

Chemical Name: Antineoplastic Agents, Phytogenic; Terpenes; limonene; Prednisolone; **Glucose** ; Isoniazid

31/5,K/14 (Item 2 from file: 155)

07132993 91374207 PMID: 1895166

Thermal enhancement **of ACNU and potentiation of thermochemotherapy with ACNU by hypertonic** glucose **in the BT4An rat glioma.**

Schem B C; Dahl O
Department of Oncology, Haukeland Hospital, University of Bergen, Norway.

Journal of neuro-oncology (NETHERLANDS) Jun **1991** , 10 (3) p247-52, ISSN 0167-594X Journal Code: 8309335
Document type: Journal Article
Languages: ENGLISH
Main Citation Owner: NLM
Record type: Completed
Subfile: INDEX MEDICUS

Hyperthermia **increases** the cytotoxicity of the nitrosourea BCNU (carmustine). **Glucose** given before treatment may further **increase** the value of thermochemotherapy, presumably by lowering tumour pH through blood flow reduction. The water-soluble ACNU (nimustine) is an alternative to other nitrosoureas in the treatment of gliomas. The drug is soluble without use of **ethanol** , and the eye complications when given intra-arterially are reduced compared with similar use of BCNU. The influence of simultaneous hyperthermia on treatment with ACNU, and the value of **glucose** administered before thermochemotherapy therefore were investigated in the malignant rat glioma BT4An. BD IX rats with subcutaneous BT4An tumours on the hind leg were treated with ACNU (i.p.), or ACNU and locally applied waterbath hyperthermia (44 degrees C for 45 min), with or without previous **glucose** (6 g/kg i.p. 2 hours before treatment). ACNU (10 or 20 mg/kg) alone and ACNU (20 mg/kg) after previous **glucose** did not influence tumour growth, compared to the controls. Simultaneous ACNU (10 mg/kg) and hyperthermia clearly was more effective than treatment with hyperthermia alone. **Glucose** load before treatment further **enhanced** the effect of combined ACNU and hyperthermia. **Glucose** before treatment did not change local toxicity or weight profiles of treatment with ACNU alone, or simultaneous ACNU and hyperthermia. **Glucose** load therefore represented a therapeutic gain when administered before thermochemotherapy with ACNU.

Tags: Animal; Comparative Study; Support, Non-U.S. Gov't
Descriptors: Brain Neoplasms; *Glioma--therapy--TH; * **Glucose** --administration and dosage--AD; *Hyperthermia, Induced; *Nimustine --therapeutic use--TU; Carmustine--therapeutic use--TU; Carmustine --toxicity--TO; Combined Modality Therapy; Drug Screening Assays, Antitumor ; Drug Synergism; Glioma--drug therapy--DT; **Glucose** --pharmacology--PD; Hydrogen-Ion **Concentration** ; Hypertonic Solutions-- **administration** and dosage--AD; Hypertonic Solutions--pharmacology--PD; Neoplasm Transplantation; Nimustine--toxicity--TO; Rats; Rats, Inbred Strains; Retinal Diseases--chemically induced--CI; **Skin** Neoplasms--drug therapy --DT; **Skin** Neoplasms--therapy--TH; Tumor Cells, Cultured --transplantation--TR
CAS Registry No.: 0 (Hypertonic Solutions); 154-93-8 (Carmustine); 42471-28-3 (Nimustine); **50-99-7 (Glucose)**
Record Date Created: 19911022
Record Date Completed: 19911022

Thermal enhancement **of ACNU and potentiation of thermochemotherapy with ACNU by hypertonic** glucose **in the BT4An rat glioma.**
Jun **1991** ,
Hyperthermia **increases** the cytotoxicity of the nitrosourea BCNU (carmustine). **Glucose** given before treatment may further **increase** the value of thermochemotherapy, presumably by lowering tumour pH through blood flow reduction. The water...

... to other nitrosoureas in the treatment of gliomas. The drug is soluble without use of **ethanol** , and the eye complications when given intra-arterially are reduced compared with similar use of BCNU. The influence of simultaneous hyperthermia on treatment with ACNU, and the value of **glucose** administered before thermochemotherapy therefore were investigated in the malignant rat glioma BT4An. BD IX rats...
... and locally applied waterbath hyperthermia (44 degrees C for 45 min), with or without previous **glucose** (6 g/kg i.p. 2 hours before treatment). ACNU (10 or 20 mg/kg) alone and ACNU (20 mg/kg) after previous **glucose** did not influence tumour growth, compared to the controls. Simultaneous ACNU (10 mg/kg) and hyperthermia clearly was more effective than treatment with hyperthermia alone. **Glucose** load before treatment further **enhanced** the effect of combined ACNU and hyperthermia. **Glucose** before treatment did not change local toxicity or weight profiles of treatment with ACNU alone, or simultaneous ACNU and hyperthermia. **Glucose** load therefore represented a therapeutic gain when administered before thermochemotherapy with ACNU.
Descriptors: Brain Neoplasms; *Glioma--therapy--TH; * **Glucose** --administration and dosage--AD; *Hyperthermia, Induced; *Nimustine --therapeutic use--TU...; toxicity--TO; Combined Modality Therapy; Drug Screening Assays, Antitumor; Drug Synergism; Glioma--drug therapy--DT; **Glucose** --pharmacology--PD; Hydrogen-Ion **Concentration** ; Hypertonic Solutions-- **administration** and dosage--AD; Hypertonic Solutions --pharmacology--PD; Neoplasm Transplantation; Nimustine--toxicity--TO; Rats ; Rats, Inbred Strains; Retinal Diseases--chemically induced--CI; **Skin** Neoplasms--drug therapy--DT; **Skin** Neoplasms--therapy--TH; Tumor Cells, Cultured--transplantation--TR
CAS Registry No.: 0 (Hypertonic Solutions); 154-93-8 (Carmustine); 42471-28-3 (Nimustine); **50-99-7 (Glucose)**
Chemical Name: Hypertonic Solutions; Carmustine; Nimustine; **Glucose**

31/5,K/15 (Item 3 from file: 155)
DIALOG(R)File 155:MEDLINE(R)

07095967 91337000 PMID: 1651701

Lipid peroxidation in electroporated **hepatocytes occurs much more readily than does hydroxyl-radical formation.**

Hallinan T; Gor J; Rice-Evans C A; Stanley R; O'Reilly R; Brown D

Department of Biochemistry, Royal Free Hospital School of Medicine, London, U.K.

Biochemical journal (ENGLAND) Aug 1 **1991** , 277 (Pt 3) p767-71, ISSN 0264-6021 Journal Code: 2984726R

Document type: Journal Article

Languages: ENGLISH

Main Citation Owner: NLM

Record type: Completed

Subfile: INDEX MEDICUS

1. Rat hepatocytes suspended in 0.25 M-sucrose were electropermeabilized. This completely disrupted their plasma-membrane **permeability barrier** . 2. The endoplasmic reticulum in **electroporated** hepatocytes appeared morphologically preserved and maintained its **permeability barrier** as evidenced by electron-microscopic examination and latency measurements on luminal reticular enzymes. 3. Upon aerobic incubation with an NADPH-generating system and iron/ADP, porated hepatocytes peroxidized their membrane lipids at rates similar to those of matched microsomal preparations. 4. When hepatocytes were incubated with iron/EDTA and azide, radical formation detectable with dimethyl sulphoxide (**DMSO**) was only 10-20% that shown by microsomes. Omitting azide abolished hepatocyte reactivity with **DMSO** completely. Effects of hydroxyl-radical (.OH) scavengers and of added catalase suggest that the radical detected by **DMSO** is .OH. 5. Cytosolic inhibitor(s) from hepatocytes seemed to be a major factor limiting .OH formation. These were macromolecular, but showed a degree of heat-stability. Dialysis largely abolished inhibition, but this could be restored again by adding GSH. 6. Since .OH formation in hepatocytes seems to be much more stringently prevented than lipid peroxidation, free-radical damage originating from intracellular redox systems seems more likely to take the form of lipid peroxidation.

Tags: Animal; Male; Support, Non-U.S. Gov't

Descriptors: *Hydroxides--chemistry--CH; *Lipid Peroxides--metabolism--ME ; *Liver--metabolism--ME; *Microsomes, Liver--metabolism--ME; Cell Membrane **Permeability** ; Cytosol--metabolism--ME; Electricity; Endoplasmic Reticulum --enzymology--EN; Free Radicals; **Glucose** -6-Phosphatase--metabolism--ME; Glucuronosyltransferase--metabolism--ME; Hydroxides--metabolism--ME; Rats; Rats, Inbred Strains

CAS Registry No.: 0 (Free Radicals); 0 (Hydroxides); 0 (Lipid Peroxides)

Enzyme No.: EC 2.4.1.17 (Glucuronosyltransferase); EC 3.1.3.9 (**Glucose** -6-Phosphatase)

Record Date Created: 19910917

Record Date Completed: 19910917

Lipid peroxidation in electroporated **hepatocytes occurs much more readily than does hydroxyl-radical formation.**

Aug 1 **1991** ,

... hepatocytes suspended in 0.25 M-sucrose were electropermeabilized. This completely disrupted their plasma-membrane **permeability barrier** . 2. The endoplasmic reticulum in **electroporated** hepatocytes appeared morphologically preserved and maintained its **permeability barrier** as evidenced by electron-microscopic examination and latency measurements on luminal reticular enzymes. 3. Upon...

... When hepatocytes were incubated with iron/EDTA and azide, radical formation detectable with dimethyl sulphoxide (**DMSO**) was only 10-20% that

shown by microsomes. Omitting azide abolished hepatocyte reactivity with **DMSO** completely. Effects of hydroxyl-radical (.OH) scavengers and of added catalase suggest that the radical detected by **DMSO** is .OH. 5. Cytosolic inhibitor(s) from hepatocytes seemed to be a major factor limiting...

; Cell Membrane **Permeability** ; Cytosol--metabolism--ME; Electricity; Endoplasmic Reticulum--enzymology--EN; Free Radicals; **Glucose** -6-Phosphatase--metabolism--ME; Glucuronosyltransferase--metabolism--ME; Hydroxides--metabolism--ME; Rats; Rats, Inbred Strains

Enzyme No.: EC 2.4.1.17 (Glucuronosyltransferase); EC 3.1.3.9 (**Glucose** -6-Phosphatase)

Chemical Name: Free Radicals; Hydroxides; Lipid Peroxides; Glucuronosyltransferase; **Glucose** -6-Phosphatase

31/5,K/16 (Item 1 from file: 35)

01257087 ORDER NO: AAD92-37992

OPTIMIZATION OF IONTOPHORETIC TRANSDERMAL DELIVERY OF A PEPTIDE AND A NON-PEPTIDE DRUG (PEPTIDE DRUG, ENALAPRILAT, CROMOLYN SODIUM)

Author: GUPTA, SANJEEV KUMAR

Degree: PH.D.
Year: **1992**
Corporate Source/Institution: ST. JOHN'S UNIVERSITY (0192)
Source: VOLUME 53/08-B OF DISSERTATION ABSTRACTS INTERNATIONAL. PAGE 4053. 160 PAGES
Descriptors: HEALTH SCIENCES, PHARMACY; CHEMISTRY, ANALYTICAL; CHEMISTRY, PHARMACEUTICAL
Descriptor Codes: 0572; 0486; 0491

Optimization studies for in vitro cathodic **iontophoretic** transdermal delivery (ITD) of a tripeptide, Enalaprilat (EP) and a non-peptide, Cromolyn sodium (CS), across hairless guinea pig (HGP) **skin** were investigated. HPLC assay methods were developed to estimate the drugs in the receptor medium. Effect of freezing of HGP skins was evaluated. The formulation parameters studied included the influence of ionic strength (μ), types of buffers, drug loading, chemical **enhancers** , conducting gels in the donor and effect of pH on EP **permeability** .

Frozen **skin** was similar to the fresh **skin** based on the flux values of both drugs. Storage of frozen **skin** did not affect the permeation of CS. Optimum μ (6.66 $\times$ 10$\sp{-3}$M) of acetate buffer was found necessary for efficient ITD of CS. **Increasing** the μ of acetate buffer, decreased the flux of CS exponentially. Less than detectable amounts permeated by **increasing** the μ ($>$31 $\times$ 10$\sp{-3}$M) of aqueous EP solution in phosphate buffer. Buffer ions larger than acetate ions inhibited the flow of cromolyn ions across the aqueous channels (pores) of **stratum corneum** due to the blocking effect. An **increase** in pH above 3.55 (pk$\sb{\rm a1}$), decreased the flux of EP linearly.

A hyperbolic relationship of the flux versus CS concentration was observed. This phenomenon was modelled based on the Michaelis-Menten enzyme kinetics which supported the fact that the **increase** in current level **increases** the **permeability** of drugs due to **increase** in number and size of pores in the **skin** . Similarly, **better** permeation of EP was obtained at higher drug loading. Passive permeation of either drug was negligible. Reversibility studies showed that the **skin** was not damaged by ITD.

A saturated CS concentration in 80:20 mixture of **ethanol** -water produced an overall flux **enhancement** , which was an additive effect of ITD and passive **enhancer** (**ethanol**) effect. Chemical **enhancers** , such as

anionic surfactants, inhibited the transport of CS across the **skin** . Different dielectric constants of propylene glycol-water combinations did not affect the flux of CS. Aqueous **glycerol** solution was ineffective for ITD.

Conducting gels of ionic polymers significantly decreased the flux of CS. However, conducting gels of non-ionic polymers were found suitable for ITD of CS. The optimized solution formulation was incorporated in a commercially available electropatch which provided $\sim$18 times higher ITD of CS compared to the electropatch containing non-optimized solution. Therapeutic levels of CS and EP in humans may be achieved by this modern non-invasive drug-delivery route.

OPTIMIZATION OF IONTOPHORETIC **TRANSDERMAL DELIVERY OF A PEPTIDE AND A NON-PEPTIDE DRUG (PEPTIDE DRUG, ENALAPRILAT, CROMOLYN SODIUM)**
Year: **1992**

Optimization studies for in vitro cathodic **iontophoretic** transdermal delivery (ITD) of a tripeptide, Enalaprilat (EP) and a non-peptide, Cromolyn sodium (CS), across hairless guinea pig (HGP) **skin** were investigated. HPLC assay methods were developed to estimate the drugs in the receptor medium...

...parameters studied included the influence of ionic strength (μ), types of buffers, drug loading, chemical **enhancers** , conducting gels in the donor and effect of pH on EP **permeability** .

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...than acetate ions inhibited the flow of cromolyn ions across the aqueous channels (pores) of **stratum corneum** due to the blocking effect. An **increase** in pH above 3.55 (pk$\sb{\rm a1}$), decreased the flux of EP linearly...

...was modelled based on the Michaelis-Menten enzyme kinetics which supported the fact that the **increase** in current level **increases** the **permeability** of drugs due to **increase** in number and size of pores in the **skin** . Similarly, **better** permeation of EP was obtained at higher drug loading. Passive permeation of either drug was negligible. Reversibility studies showed that the **skin** was not damaged by ITD.

A saturated CS concentration in 80:20 mixture of **ethanol** -water produced an overall flux **enhancement** , which was an additive effect of ITD and passive **enhancer** (**ethanol**) effect. Chemical **enhancers** , such as anionic surfactants, inhibited the transport of CS across the **skin** . Different dielectric constants of propylene glycol-water combinations did not affect the flux of CS. Aqueous **glycerol** solution was ineffective for ITD.

Conducting gels of ionic polymers significantly decreased the flux of ...

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Set     Items   Description
S1          1   AU=(NEMATI B? OR NEMATI, B? OR NEMATI B OR NEMATI, B OR NE-
              MATI B. OR NEMATI, B. OR NEMATI BABAK OR NEMATI, BABAK)
? show files
File 347:JAPIO Oct 1976-2003/Aug(Updated 031202)
         (c) 2003 JPO & JAPIO
File 350:Derwent WPIX 1963-2003/UD,UM &UP=200378
         (c) 2003  Thomson Derwent
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1/3,AU/1 (Item 1 from file: 350)
DIALOG(R)File 350:Derwent WPIX

013178732
WPI Acc No: 2000-350605/200030
XRAM Acc No: C00-106644
XRPX Acc No: N00-262704

Novel method of enhancing optical transparency of biological tissue covered by surface barrier by bypassing the barrier, e.g. by abrasion, useful for treating skin appendages and detecting blood glucose

Patent Assignee: NEMATI B (NEMA-I)
Inventor: **NEMATI B**
Number of Countries: 029 Number of Patents: 007
Patent Family:

Patent No	Kind	Date	Applicat No	Kind	Date	Week
WO 200024454	A1	20000504	WO 99US23526	A	19991012	200030 B
AU 9964228	A	20000515	AU 9964228	A	19991012	200039
EP 1045717	A1	20001025	EP 99951881	A	19991012	200055
			WO 99US23526	A	19991012	
US 6219575	B1	20010417	US 98177348	A	19981023	200123
US 20010008959	A1	20010719	US 98177348	A	19981023	200143
			US 2001777639	A	20010207	
US 20010009984	A1	20010726	US 98177348	A	19981023	200146
			US 2001777640	A	20010207	
AU 753574	B	20021024	AU 9964228	A	19991012	200277

Priority Applications (No Type Date): US 98177348 A 19981023; US 2001777639 A 20010207; US 2001777640 A 20010207
Patent Details:

Patent No	Kind	Lan	Pg	Main IPC	Filing Notes
WO 200024454	A1	E	46	A61N-001/30	
Designated States (National): AU BR CA CZ FI JP MX NO SG					
Designated States (Regional): AT BE CH CY DE DK EA ES FI FR GB GR IE IT LU MC NL PT SE					
AU 9964228	A			A61N-001/30	Based on patent WO 200024454
EP 1045717	A1	E		A61N-001/30	Based on patent WO 200024454
Designated States (Regional): AT BE CH CY DE DK ES FI FR GB GR IE IT LI LU MC NL PT SE					
US 6219575	B1			A61N-001/30	
US 20010008959	A1			A61N-001/30	Div ex application US 98177348 Div ex patent US 6219575
US 20010009984	A1			A61N-001/30	Div ex application US 98177348 Div ex patent US 6219575
AU 753574	B			A61N-001/30	Previous Publ. patent AU 9964228 Based on patent WO 200024454

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Set     Items   Description
S1          2   AU=(NEMATI B? OR NEMATI, B? OR NEMATI B OR NEMATI, B OR NE-
              MATI B. OR NEMATI, B. OR NEMATI BABAK OR NEMATI, BABAK)
? show files
File 348:EUROPEAN PATENTS 1978-2003/Nov W04
         (c) 2003 European Patent Office
File 349:PCT FULLTEXT 1979-2002/UB=20031127,UT=20031120
         (c) 2003 WIPO/Univentio
```

1/3,AU/1 **(Item 1 from file: 348)**
DIALOG(R)File 348:EUROPEAN PATENTS

01164177
ENHANCING OPTICAL TRANSPARENCY OF BIOLOGICAL TISSUE
VERBESSERUNG OPTISCHER TRANSPARENZ VON BIOLOGISCHEM GEWEBE
AMELIORATION DE LA TRANSPARENCE OPTIQUE ET TISSU BIOLOGIQUE
PATENT ASSIGNEE:
Nemati, Babak, (3016330), 5313 Town Court South, Lawrenceville, NJ 08648, (US), (Applicant designated States: all)
INVENTOR:
Nemati, Babak , 5313 Town Court South, Lawrenceville, NJ 08648, (US
LEGAL REPRESENTATIVE:
Fuchs Mehler Weiss & Fritzsche (100495), Patentanwalte
Abraham-Lincoln-Strasse 7, 65189 Wiesbaden, (DE)
PATENT (CC, No, Kind, Date): EP 1045717 A1 001025 (Basic)
WO 0024454 000504
APPLICATION (CC, No, Date): EP 99951881 991012; WO 99US23526 991012
PRIORITY (CC, No, Date): US 177348 981023
DESIGNATED STATES: AT; BE; CH; CY; DE; DK; ES; FI; FR; GB; GR; IE; IT; LI; LU; MC; NL; PT; SE
INTERNATIONAL PATENT CLASS: A61N-001/30
NOTE:
No A-document published by EPO
LANGUAGE (Publication,Procedural,Application): English; English; English

1/3,AU/2 **(Item 1 from file: 349)**
DIALOG(R)File 349:PCT FULLTEXT

00561081
ENHANCING OPTICAL TRANSPARENCY OF BIOLOGICAL TISSUE
AMELIORATION DE LA TRANSPARENCE OPTIQUE ET TISSU BIOLOGIQUE
Patent Applicant/Assignee:
NEMATI Babak,
Inventor(s):
NEMATI Babak
Patent and Priority Information (Country, Number, Date):
Patent: WO 200024454 A1 20000504 (WO 0024454)
Application: WO 99US23526 19991012 (PCT/WO US9923526)
Priority Application: US 98177348 19981023
Designated States: AU BR CA CZ FI JP MX NO SG AM AZ BY KG KZ MD RU TJ TM AT BE CH CY DE DK ES FI FR GB GR IE IT LU MC NL PT SE
Publication Language: English
Fulltext Word Count: 8746

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Set     Items   Description
S1        342   AU=(NEMATI B? OR NEMATI, B? OR NEMATI B OR NEMATI, B OR NE-
              MATI B. OR NEMATI, B. OR NEMATI BABAK OR NEMATI, BABAK)
S2          0   S1 AND CLARIF?()AGENT? AND ENHANC?()AGENT?
S3         31   S1 AND OPTIC?
S4         16   S3 AND PY<1999
? show files
File   5:Biosis Previews(R) 1969-2003/Nov W5
         (c) 2003 BIOSIS
File   6:NTIS 1964-2003/Nov W5
         (c) 2003 NTIS, Intl Cpyrght All Rights Res
File  34:SciSearch(R) Cited Ref Sci 1990-2003/Nov W5
         (c) 2003 Inst for Sci Info
File  65:Inside Conferences 1993-2003/Nov W5
         (c) 2003 BLDSC all rts. reserv.
File  71:ELSEVIER BIOBASE 1994-2003/Nov W5
         (c) 2003  Elsevier Science B.V.
File  73:EMBASE 1974-2003/Nov W5
         (c) 2003 Elsevier Science B.V.
File  94:JICST-EPlus 1985-2003/Nov W5
         (c)2003 Japan Science and Tech Corp(JST)
File 144:Pascal 1973-2003/Nov W4
         (c) 2003 INIST/CNRS
File 155:MEDLINE(R) 1966-2003/Nov W4
         (c) format only 2003 The Dialog Corp.
File 434:SciSearch(R) Cited Ref Sci 1974-1989/Dec
         (c) 1998 Inst for Sci Info
File  35:Dissertation Abs Online 1861-2003/Oct
         (c) 2003 ProQuest Info&Learning
File  91:MANTIS(TM) 1880-2002/Dec
         2003 (c) Action Potential
File   2:INSPEC 1969-2003/Nov W4
         (c) 2003 Institution of Electrical Engineers
File   8:Ei Compendex(R) 1970-2003/Nov W4
         (c) 2003 Elsevier Eng.  Info. Inc.
File  95:TEME-Technology & Management 1989-2003/Nov W3
         (c) 2003 FIZ TECHNIK
File  99:Wilson Appl. Sci & Tech Abs 1983-2003/Oct
         (c) 2003 The HW Wilson Co.
? pause
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4/3,AU/1 (Item 1 from file: 5)
DIALOG(R)File 5:Biosis Previews(R)

0008040465 BIOSIS NO.: 199243009056
OPTICAL **PROPERTIES OF CONJUNCTIVA SCLERA AND CILIARY BODY AND THEIR CONSEQUENCES FOR TRANSSCLERAL CYCLOPHOTOCOAGULATION**
AUTHOR: **NEMATI B** (Reprint); RYLANDER H G III; WELCH A J
AUTHOR ADDRESS: MED OPTICS LAB, BIOMED ENGINEERING PROGRAM, UNIVERSITY TEXAS AUSTIN, AUSTIN, TEXAS 78712, USA**USA
JOURNAL: Lasers in Surgery and Medicine (SUPPL. 4): p54 **1992**
CONFERENCE/MEETING: TWELFTH ANNUAL MEETING OF THE AMERICAN SOCIETY FOR LASER MEDICINE AND SURGERY, LAKE BUENA VISTA, FLORIDA, USA, MAY 17-19, 1992. LASERS SURG MED.
ISSN: 0196-8092
DOCUMENT TYPE: Meeting
RECORD TYPE: Citation
LANGUAGE: ENGLISH

4/3,AU/2 (Item 1 from file: 34)
DIALOG(R)File 34:SciSearch(R) Cited Ref Sci

06472701 Genuine Article#: YV841 Number of References: 24
Title: Optical **model for light distribution during transscleral cyclophotocoagulation** (ABSTRACT AVAILABLE)
Author(s): **Nemati B (REPRINT)** ; Dunn A; Welch AJ; Rylander HG
Corporate Source: ETHICON INC,POB 151/SOMERVILLE//NJ/08876 (REPRINT); UNIV TEXAS,BIOMED ENGN PROGRAM, MED OPT LAB/AUSTIN//TX/78712
Journal: APPLIED OPTICS, **1998** , V37, N4 (FEB 1), P764-771
ISSN: 0003-6935 Publication date: 19980201
Publisher: OPTICAL SOC AMER, 2010 MASSACHUSETTS AVE NW, WASHINGTON, DC 20036
Language: English Document Type: ARTICLE

4/3,AU/3 (Item 2 from file: 34)
DIALOG(R)File 34:SciSearch(R) Cited Ref Sci

05504976 Genuine Article#: WD153 Number of References: 1
Title: Optical **properties of conjunctiva, sclera, and the ciliary body and their consequences for transscleral cyclophotocoagulation (vol 35, pg 3321, 1996)**
Author(s): **Nemati B (REPRINT)** ; Rylander HG; Welch A
Corporate Source: CANDELA CORP,530 BOSTON POST RD/WAYLAND//MA/01778 (REPRINT); UNIV TEXAS,BIOMED ENGN PROGRAM, BIOMED ENGN LASER LAB/AUSTIN//TX/78712
Journal: APPLIED OPTICS, **1997** , V36, N1 (JAN 1), P416-416
ISSN: 0740-3224 Publication date: 19970101
Publisher: OPTICAL SOC AMER, 2010 MASSACHUSETTS AVE NW, WASHINGTON, DC 20036
Language: English Document Type: CORRECTION, ADDITION

4/3,AU/4 (Item 3 from file: 34)
DIALOG(R)File 34:SciSearch(R) Cited Ref Sci

04973133 Genuine Article#: UW460 Number of References: 25
Title: OPTICAL **-PROPERTIES OF CONJUNCTIVA, SCLERA, AND THE CILIARY BODY AND THEIR CONSEQUENCES FOR TRANSSCLERAL CYCLOPHOTOCOAGULATION** (Abstract Available)
Author(s): **NEMATI B** ; RYLANDER HG; WELCH AJ
Corporate Source: UNIV TEXAS,BIOMED ENGN PROGRAM,BIOMED ENGN LASER LAB/AUSTIN//TX/78712
Journal: APPLIED OPTICS, **1996** , V35, N19 (JUL 1), P3321-3327
ISSN: 0003-6935
Language: ENGLISH Document Type: ARTICLE

4/3,AU/5 (Item 1 from file: 65)
DIALOG(R)File 65:Inside Conferences

02549874 INSIDE CONFERENCE ITEM ID: CN026590140
Starlight beam misalignment in optical **synthesis imaging (3356-111)**
Nemati, B. ; Duncan, A. L.
CONFERENCE: Space telescopes and instruments-Conference; 5th
PROCEEDINGS-SPIE THE INTERNATIONAL SOCIETY FOR OPTICAL ENGINEERING, 1998 ; ISSUE 3356; NUMBER 1 P: 670-677
SPIE, **1998**
ISSN: 0277-786X ISBN: 0819428035
LANGUAGE: English DOCUMENT TYPE: Conference Papers
CONFERENCE EDITOR(S): Bely, P. Y.; Breckinridge, J. B.
CONFERENCE SPONSOR: SPIE
CONFERENCE DATE: Mar 1998 (199803) (199803)

NOTE:
Held on the island of Kona, HI

4/3,AU/6 (Item 2 from file: 65)
DIALOG(R)File 65:Inside Conferences

02461004 INSIDE CONFERENCE ITEM ID: CN025701449
Laser soft-palate stiffening (3245-25)
Wang, Z.; McMillan, K.; Perrault, D. F.; **Nemati, B.**
CONFERENCE: Lasers in surgery: advanced characterization, therapeutics, and systems VIII-Conference
PROCEEDINGS-SPIE THE INTERNATIONAL SOCIETY FOR OPTICAL ENGINEERING, 1998 ; ISSUE 3245 P: 136-144
SPIE, **1998**
ISSN: 0277-786X ISBN: 0819426849
LANGUAGE: English DOCUMENT TYPE: Conference Papers
CONFERENCE EDITOR(S): Anderson, R. R.
CONFERENCE SPONSOR: SPIE
International Biomedical Optics Society
CONFERENCE LOCATION: San Jose, CA
CONFERENCE DATE: Jan 1998 (199801) (199801)

4/3,AU/7 (Item 3 from file: 65)
DIALOG(R)File 65:Inside Conferences

00455663 INSIDE CONFERENCE ITEM ID: CN004373947
Optical **model for the propagation of light during transscleral**

cyclophotocoagulation [2126-32]
Nemati, B. ; Rylander, H. G.; Welch, A. J.
CONFERENCE: Ophthalmic technologies IV-Conference
PROCEEDINGS- SPIE THE INTERNATIONAL SOCIETY FOR OPTICAL ENGINEERING, 1994; ISSUE 2126 P: 251-258
SPIE, **1994**
ISSN: 0361-0748 ISBN: 0819414190
LANGUAGE: English DOCUMENT TYPE: Conference Papers
CONFERENCE EDITOR(S): Parel, J. M.; Ren, Q.
CONFERENCE SPONSOR: SPIE
CONFERENCE LOCATION: Los Angeles, CA
CONFERENCE DATE: Jan 1994 (199401) (199401)

4/3,AU/8 (Item 1 from file: 144)
DIALOG(R)File 144:Pascal
(c) 2003 INIST/CNRS. All rts. reserv.

13489585 PASCAL No.: 98-0187077
Optical **model for light distribution during transscleral cyclophotocoagulation**
NEMATI Babak ; DUNN Andrew; WELCH Ashely J; RYLANDER H Grady
Medical Optics Laboratory, Biomedical Engineering Program, ENS 610, University of Texas, Austin, Texas 78712
Journal: Applied optics, **1998** -02-01, 37 (4) 764-771
Language: English

4/3,AU/9 (Item 2 from file: 144)
DIALOG(R)File 144:Pascal
(c) 2003 INIST/CNRS. All rts. reserv.

13374911 PASCAL No.: 97-0560306
Optical **properties of conjunctiva, sclera, and the ciliary body and their consequences for transscleral cyclophotocoagulation: erratum**
NEMATI Babak ; RYLANDER H Grady; WELCH Ashley
Biomedical Engineering Laser Laboratory, Biomedical Engineering Program, University of Texas at Austin, Austin, Texas 78712; Candela Corporation, 530 Boston Post Road, Wayland, Massachusetts 01778
Journal: Applied optics, **1997** -01-01, 36 (1) p. 416
Language: English

4/3,AU/10 (Item 3 from file: 144)
DIALOG(R)File 144:Pascal
(c) 2003 INIST/CNRS. All rts. reserv.

13122685 PASCAL No.: 97-0104831
Optical **properties of conjunctiva, sclera, and the ciliary body and their consequences for transscleral cyclophotocoagulation**
NEMATI B ; RYLANDER III H G; WELCH A J
Biomedical Engineering Laser Laboratory, Biomedical Engineering Program, University of Texas at Austin, Austin, Texas 78712
Journal: Applied optics, **1996** -07-01, 35 (19) 3321-3327
Language: English

4/3,AU/11 (Item 1 from file: 35)
DIALOG(R)File 35:Dissertation Abs Online

01440235 AADAAI9534909
TRANSSCLERAL ARGON CYCLOPHOTOCOAGULATION: A PRECLINICAL FEASIBILITY STUDY (GLAUCOMA)
Author: **NEMATI, BABAK**
Degree: PH.D.
Year: **1995**
Corporate Source/Institution: THE UNIVERSITY OF TEXAS AT AUSTIN (0227)
Source: VOLUME 56/06-B OF DISSERTATION ABSTRACTS INTERNATIONAL.
PAGE 3317. 505 PAGES

4/3,AU/12 (Item 1 from file: 2)
DIALOG(R)File 2:INSPEC

5850844 INSPEC Abstract Number: A9808-8760F-001, B9804-7520C-011
Title: Optical **model for light distribution during transscleral cyclophotocoagulation**
Author(s): **Nemati, B.** ; Dunn, A.; Welch, A.J.; Rylander, H.G., III
Author Affiliation: Med. Opt. Lab., Texas Univ., Austin, TX, USA
Journal: Applied Optics vol.37, no.4 p.764-71
Publisher: Opt. Soc. America,
Publication Date: 1 Feb. 1998 Country of Publication: USA
CODEN: APOPAI ISSN: 0003-6935
SICI: 0003-6935(19980201)37:4L.764:OMLD;1-A
Material Identity Number: A132-98006
U.S. Copyright Clearance Center Code: 0003-6935/98/040764-08$10.00/0
Language: English
Subfile: A B

4/3,AU/13 (Item 2 from file: 2)
DIALOG(R)File 2:INSPEC

5348028 INSPEC Abstract Number: A9619-8732C-001, B9610-7520C-002
Title: Optical **properties of conjunctiva, sclera, and the ciliary body and their consequences for transscleral cyclophotocoagulation**
Author(s): **Nemati, B.** ; Rylander, H.G., III; Welch, A.J.
Author Affiliation: Biomed. Eng. Laser Lab., Texas Univ., Austin, TX, USA
Journal: Applied Optics vol.35, no.19 p.3321-7
Publisher: Opt. Soc. America,
Publication Date: 1 July 1996 Country of Publication: USA
CODEN: APOPAI ISSN: 0003-6935
SICI: 0003-6935(19960701)35:19L.3321:OPCS;1-H
Material Identity Number: A132-96022
U.S. Copyright Clearance Center Code: 0003-6935/96/193321-07$10.00/0
Language: English
Subfile: A B

4/3,AU/14 (Item 1 from file: 8)
DIALOG(R)File 8:Ei Compendex(R)

05219567
E.I. No: EIP99024554001
Title: Starlight beam misalignment in optical **synthesis imaging**
Author: **Nemati, Bijan** ; Duncan, Alan
Corporate Source: Lockheed Martin Missiles and Space, Palo Alto, CA, USA
Conference Title: Proceedings of the 1998 Conference on Space Telescopes and Instruments V. Part 1 (of 2)
Conference Location: Kona, HI, USA Conference Date: 19980325-19980328
E.I. Conference No.: 49620
Source: Proceedings of SPIE - The International Society for Optical Engineering 3356 1 1998. SPIE, Bellingham, WA, USA. p 670-677
Publication Year: 1998
CODEN: PSISDG ISSN: 0277-786X
Language: English

4/3,AU/15 (Item 1 from file: 99)
DIALOG(R)File 99:Wilson Appl. Sci & Tech Abs

1632018 H.W. WILSON RECORD NUMBER: BAST98014034
Optical **model for light distribution during transscleral cyclophotocoagulation**
Nemati, Babak ; Dunn, Andrew; Welch, Ashley J
Applied Optics v. 37 (Feb. 1 '98) p. 764-71
DOCUMENT TYPE: Feature Article ISSN: 0003-6935

4/3,AU/16 (Item 2 from file: 99)
DIALOG(R)File 99:Wilson Appl. Sci & Tech Abs

1416711 H.W. WILSON RECORD NUMBER: BAST96045410
Optical **properties of conjunctiva, sclera, and the ciliary body and their consequences for transscleral cyclophotocoagulation**
Nemati, Babak ; Rylander, H. Grady III; Welch, Ashley J
Applied Optics v. 35 (July 1 '96) p. 3321-7
DOCUMENT TYPE: Feature Article ISSN: 0003-6935

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Set     Items   Description
S1          0   AU=(NEMATI B? OR NEMATI, B? OR NEMATI B OR NEMATI, B OR NE-
             MATI B. OR NEMATI, B. OR NEMATI BABAK OR NEMATI, BABAK)
? show files
File  98:General Sci Abs/Full-Text 1984-2003/Oct
         (c) 2003 The HW Wilson Co.
File 369:New Scientist 1994-2003/Nov W5
         (c) 2003 Reed Business Information Ltd.
File 370:Science 1996-1999/Jul W3
         (c) 1999 AAAS
File 444:New England Journal of Med. 1985-2003/Dec W1
         (c) 2003 Mass. Med. Soc.
File 482:Newsweek 2000-2003/Dec 03
         (c) 2003 Newsweek, Inc.
File 135:NewsRx Weekly Reports 1995-2003/Nov W5
         (c) 2003 NewsRx
File 441:ESPICOM Pharm&Med DEVICE NEWS 2003/Nov W5
         (c) 2003 ESPICOM Bus.Intell.
File  16:Gale Group PROMT(R) 1990-2003/Dec 04
         (c) 2003 The Gale Group
File 160:Gale Group PROMT(R) 1972-1989
         (c) 1999 The Gale Group
File 621:Gale Group New Prod.Annou.(R) 1985-2003/Dec 04
         (c) 2003 The Gale Group
File 743:(New Jersey)The Record 1989-2003/Dec 04
         (c) 2003 No.Jersey Media G Inc
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Set     Items   Description
S1     105628   ENHANC?()AGENT? OR DMSO OR ETHANOL OR PENETRAT?()SOLVENT? -
            OR (SULPHUR? OR SULFUR?)()COMPOUND?()SOLVENT?
S2          0   RN=67-68-5
S3          0   DC=D.02.886.640.150
S4      43472   (CLARIFY? OR CLARIFI?)()AGENT? OR GLUCOSE OR GLUCONIC OR D-
            EXTROGLUCOSE OR DEXTROSE OR DEXTRONIC OR MALTONIC
S5      58618   GLYCOGEN? OR GLYCERYL? OR GLYCERIN? OR GLYCEROL?
S6          0   DC=D09.203.546.359.448
S7          0   RN=50-99-7
S8         14   DIATRIZOATE()MEGLUMINE OR DIATRIZOATE()METHLYGLUCAMINE OR -
            DIATRIZOIC()ACID()METHYLGLUCAMINE OR MEGLUMINE()DIATRIZOATE OR
             METHYLGLUCAMINE()DIATRIZOATE OR (AMIDOTRICOIC OR AMIDOTRIZOI-
            C)()ACID? OR MEGLUMINE()AMIDOTRIZOATE
S9          0   RN=131-49-7
S10         0   DC=(D02.033.800.813.550.500 OR D02.241.223.100.140.100.375-
            .880.275 OR D09.203.037.342.600.500 OR D09.203.853.813.550.50-
            0)
S11      2954   IONTOPHORE? OR IONTOTHERAP? OR IONIC()THERAP? OR EMDA OR S-
            ONOPHORE? OR ELECTROPORAT? OR ELECTRO()PORAT?
S12         0   DC=E05.300.650
S13     93558   (DRIVING OR ELECTRIC()PULSE OR ELECTRICPULSE OR ELECTROMOT-
            IVE OR ELECTRO()MOTIVE OR ACOUSTIC? OR ULTRASONIC? OR ELECTRI-
            CAL? OR RADIOFREQUENCY? OR RADIO()FREQUENCY OR TEMPERATURE OR
            THERMAL OR PHYSICAL OR CHEMICAL OR CONCENTRATION OR E...
S14        22   (MICRONEEDLE? OR MICRO()NEEDLE?)()ARRAY? ?
S15   2045682   INCREAS? OR ENHANC? OR AMELIORAT?
S16   1478299   PERMIT? OR PERMISS? OR ALLOW?
S17   2591722   BETTER? OR IMPROV?
S18    148050   RECEPTABIL? OR PERMEABIL? OR PERMEABL? OR LUCENCY?
S19    384313   TRANSLUCEN? OR TRANSPAREN? OR CLEARNESS OR CLARITY
S20   2097892   OPTICAL? OR LIGHT? OR LUCID?
S21    158190   PERMEAB?()(BARRIER? OR LAYER? OR STRAT?) OR SKIN
S22     12494   CONJUNCTIV? OR EPITHELI? OR SCLERA? OR STRAT?()CORNE? OR (-
            INTERSTIT? OR INTER()STIT?)()(SPACE? OR TISSUE?)
S23    342574   IC=(A61N? OR A61M? OR A61B?)
S24      3882   DIMETHYL()(SULFOXIDE OR SULPHONYL) OR DIMEXIDE OR RIMSO OR
            RIMSO100 OR SULFINYL()BISMETHANE OR SULFINYLBISMETHANE
S25        85   (S1:S3 OR S24) AND S4:S10 AND S11:S14
S26        66   S25 AND S15:S23
S27        85   S25:S26
S28        13   S27 AND PY<1999
S29        13   IDPAT (sorted in duplicate/non-duplicate order)
? show files
File 347:JAPIO Oct 1976-2003/Aug(Updated 031202)
         (c) 2003 JPO & JAPIO
File 350:Derwent WPIX 1963-2003/UD,UM &UP=200378
         (c) 2003  Thomson Derwent
```

29/3,K/1 (Item 1 from file: 350)
DIALOG(R)File 350:Derwent WPIX

009782126
WPI Acc No: 1994-061979/ **199408**
XRAM Acc No: C94-027715
XRPX Acc No: N94-049042
Drug absorption accelerator for iontophoresis **- comprises electrolyte, ethanol @, water and monoterpene analogue and/or fatty acid monoglyceride**
Patent Assignee: ADVANCE KK (ADVN); JAPAN TOBACCO INC (NISB)
Number of Countries: 001 Number of Patents: 001
Patent Family:

Patent No	Kind	Date	Applicat No	Kind	Date	Week	
JP 6016538	A	19940125	JP 92198949	A	19920703	199408	B

Priority Applications (No Type Date): JP 92198949 A 19920703
Patent Details:

Patent No	Kind	Lan	Pg	Main IPC	Filing Notes
JP 6016538	A		7	A61K-009/08	

Drug absorption accelerator for iontophoresis **- ...**

...**comprises electrolyte,** ethanol **@, water and monoterpene analogue and/or fatty acid monoglyceride**
...Abstract (Basic): Drug absorption accelerating compsn. for **iontophoresis** comprises electrolyte having sufficient electro conductivity, 10-70 wt % of **ethanol** , absorption accelerator consisting of 0.5-20 wt% of monoterpene analogue and/or fatty acid...

...Ph of the compsn. is pref. 3-7. Fatty acid monoglyceride is pref. **glycerol** monoester of 6-12C medium chain fatty acid, e.g. caproic acid monoglyceride, caprylic acid...

...USE/ADVANTAGE - The compsn. aids absorption of polypeptide-type drug effectively through the **skin** even under low electric currency and low voltage. The polypeptide-type drug can be administered...
...Title Terms: **IONTOPHORESIS** ;
...International Patent Class (Additional): **A61N-001/30**

29/3,K/2 **(Item 2 from file: 347)**
DIALOG(R)File 347:JAPIO

04372638
LIQUID COMPOSITION FOR DRUG ABSORPTION FOR **IONTOPHORESIS**

PUB. NO.: 06-016538 [JP 6016538 A]
PUBLISHED: January 25, 1994 (**19940125)**
INVENTOR(s): SUNAMI MASAKI
SHINDO YORIAKI
NAKAGAWA TAKASHI
ISHIKAWA TOSHIHIRO
SUGIMORI KENICHI
OKABE KEIICHIRO
APPLICANT(s): JAPAN TOBACCO INC [000456] (A Japanese Company or Corporation), JP (Japan)
ADVANCE CO LTD [470031] (A Japanese Company or Corporation), JP (Japan)
APPL. NO.: 04-198949 [JP 92198949]
FILED: July 03, 1992 (19920703)
JOURNAL: Section: C, Section No. 1193, Vol. 18, No. 222, Pg. 24, April 21, 1994 (19940421)

LIQUID COMPOSITION FOR DRUG ABSORPTION FOR **IONTOPHORESIS**
...PUBLISHED: **19940125)**
INTL CLASS: A61K-009/08; A61K-047/10; A61K-047/14; **A61N-001/30** ; A61K-037/02

ABSTRACT
... absorption capable of effectively subjecting especially biologically active polypeptide based drugs to percutaneous absorption with **iontophoresis** .

...

...CONSTITUTION: The liquid composition for drug absorption consists of (A) 0.1-10wt.% pharmacologically **permissible** electrolyte enough to provide conductivity, e.g. sodium chloride, sodium carbonate, disodium hydrogenphosphate or citric acid, (B) 10-70wt.% **ethanol** , (C) 0.5-20wt.% monoterpenes (e.g. l-menthol, limonene or cineole) and/or a fatty acid monoglyceride, preferably a **glycerin** monoester of a 6-12C middle-chain fatty acid as an absorption promotor and (D

29/3,K/5 (Item 5 from file: 350)
DIALOG(R)File 350:Derwent WPIX

009488988 **Image available**
WPI Acc No: 1993-182523/ **199322**
XRAM Acc No: C93-080871
XRPX Acc No: N93-140303

Pressure-sensitive poly(n-polyvinyl lactam) compsn. - prepd. by irradiating solid poly(n-polyvinyl lactam) and mixing with non-irradiated plasticiser

Patent Assignee: MINNESOTA MINING & MFG CO (MINN)
Inventor: ASMUS R A; BENSON O; DIETZ T M; DUAN D C; UY R
Number of Countries: 020 Number of Patents: 012
Patent Family:

Patent No	Kind	Date	Applicat No	Kind	Date	Week
WO 9310201	A1	19930527	WO 92US9397	A	19921030	199322 B
AU 9331254	A	19930615	AU 9331254	A	19921030	199340
US 5276079	A	19940104	US 91792442	A	19911115	199402
EP 612342	A1	19940831	EP 92925054	A	19921030	199433
			WO 92US9397	A	19921030	
US 5389376	A	19950214	US 91792442	A	19911115	199512
			US 93139516	A	19931015	
JP 7501101	W	19950202	WO 92US9397	A	19921030	199514
			JP 93509290	A	19921030	
AU 657188	B	19950302	AU 9331254	A	19921030	199516
US 5409966	A	19950425	US 91792442	A	19911115	199522
			US 93137665	A	19931015	
US 5438988	A	19950808	US 91792442	A	19911115	199537
			US 93137606	A	19931015	
EP 612342	B1	19961211	EP 92925054	A	19921030	199703
			WO 92US9397	A	19921030	
DE 69215893	E	19970123	DE 615893	A	19921030	199709
			EP 92925054	A	19921030	
			WO 92US9397	A	19921030	
JP 3426231	B2	20030714	WO 92US9397	A	19921030	200347
			JP 93509290	A	19921030	

Priority Applications (No Type Date): US 91792442 A 19911115; US 93139516 A 19931015; US 93137665 A 19931015; US 93137606 A 19931015
Patent Details:

Patent No	Kind	Lan	Pg	Main IPC	Filing Notes
WO 9310201	A1	E	30	C09J-139/04	
Designated States (National): AU CA JP					
Designated States (Regional): AT BE CH DE DK ES FR GB GR IE IT LU MC NL SE					
AU 9331254	A			C09J-139/04	Based on patent WO 9310201
US 5276079	A		14	C08J-003/28	
EP 612342	A1	E		C09J-139/04	Based on patent WO 9310201
Designated States (Regional): AT BE CH DE DK ES FR GB IE IT LI NL SE					
US 5389376	A		14	A61F-013/02	Div ex application US 91792442 Div ex patent US 5276079
JP 7501101	W			C09J-139/04	Based on patent WO 9310201
AU 657188	B			C09J-139/04	Previous Publ. patent AU 9331254 Based on patent WO 9310201
US 5409966	A		13	C08J-003/28	Div ex application US 91792442 Div ex patent US 5276079
US 5438988	A		15	A61B-005/04	Div ex application US 91792442 Div ex patent US 5276079
EP 612342	B1	E	22	C09J-139/04	Based on patent WO 9310201
Designated States (Regional): AT BE CH DE DK ES FR GB IE IT LI NL SE					

DE 69215893	E		C09J-139/04	Based on patent EP 612342 Based on patent WO 9310201
JP 3426231	B2	16	C09J-139/04	Previous Publ. patent JP 7501101 Based on patent WO 9310201

...Abstract (Basic): a swelling capacity of at least 15, pref. 40ml water/g. The plasticiser is pref. **glycerin** or polyethylene glycol...
...and electrical contact with the electrical diagnostic, therapeutic or electrosurgical instrumentation. For use as a **skin** covering, the compsn. adhesive layer may comprise discrete swollen gel particles dispersed in a continuous...

...agent. For use in a pharmaceutical delivery device, the compsn. comprises a topical, transdermal, or **iontophoretic** therapeutic agent or pharmaceutical, and opt. an excipient, solvent or penetration **enhancing agent** .
...

...component of a biomedical electrode, for delivery of pharmaceuticals or active agents to or through **skin** , or for treatment of **skin** against possible infection. The method of prepn. of the compsn. minimises the presence of radiation
...Abstract (Equivalent): Biomedical electrode comprises (a) a field of adhesion conductive medium for contacting mammalian **skin** ; and (b) electrical communication for interfacing with this, and the electrical instrumentation. Medium (a) is...

...signals, as a drug delivery device for pharmaceuticals and other active ingredients in and through **skin** , etc...
...drug delivery device for delivering a pharmaceutical or other achive agent to or through manmalia **skin** .
...

...Mammalian **skin** cover comprises a support and backing film, substrate or elastic porous material, coated on one...

...USE/ADVANTAGE - The prods. are medicated tapes, wound dressings, bandages or medical **skin** covers. The prods. are free from residual monomers, by-products of chemical crosslinking agents and/or irradiated plasticiser prods., etc., avoiding antagonism of the **skin** or wound
International Patent Class (Main): **A61B-005/04** ...
International Patent Class (Additional): **A61B-005/0408** ...

... **A61N-001/04** ...

... **A61N-001/30**

29/3,K/8 (Item 8 from file: 350)
DIALOG(R)File 350:Derwent WPIX

008375768 **Image available**
WPI Acc No: 1990-262769/ **199035**
XRAM Acc No: C90-113793
XRPX Acc No: N90-203562
Conductive gel and appts. contg. it for electrical skin **treatment - which contains polyvinyl alcohol,** ethanol **and plasticiser, polymerises in air and then becomes electrically resistant**
Patent Assignee: RAMOND G (RAMO-I); LAMMON G (LAMM-I)
Inventor: RAMOND G
Number of Countries: 018 Number of Patents: 011
Patent Family:

Patent No	Kind	Date	Applicat No	Kind	Date	Week	
EP 384804	A	19900829	EP 90400379	A	19900213	199035	B
FR 2642976	A	19900817	FR 891949	A	19890215	199040	
AU 9049394	A	19900823				199041	
CA 2010082	A	19900815				199044	
JP 2241465	A	19900926	JP 9032603	A	19900215	199045	
US 5085227	A	19920204	US 90480613	A	19900215	199208	
JP 93025513	B	19930413	JP 9032603	A	19900215	199317	
AU 638431	B	19930701	AU 9049394	A	19900214	199333	
EP 384804	B1	19940504	EP 90400379	A	19900213	199418	
DE 69008583	E	19940609	DE 608583	A	19900213	199424	
			EP 90400379	A	19900213		
ES 2054280	T3	19940801	EP 90400379	A	19900213	199432	

Priority Applications (No Type Date): FR 891949 A 19890215
Patent Details:

Patent No	Kind	Lan	Pg	Main IPC	Filing Notes
EP 384804	A				
Designated States (Regional): AT BE CH DE ES GB GR IT LI LU NL SE					
JP 93025513	B		5	A61N-001/04	Based on patent JP 2241465
AU 638431	B			A61N-001/04	patent AU 9049394
EP 384804	B1	F	7	A61K-007/48	
Designated States (Regional): AT BE CH DE DK ES GB GR IT LI LU NL SE					
DE 69008583	E			A61K-007/48	Based on patent EP 384804
ES 2054280	T3			A61K-007/48	Based on patent EP 384804

Conductive gel and appts. contg. it for electrical skin **treatment...**

...**which contains polyvinyl alcohol,** ethanol **and plasticiser, polymerises in air and then becomes electrically resistant**

...Abstract (Basic): Claimed is a compsn. (I) which can be spread over an area of **skin** to **allow** application of an electric current, comprising a gel which a. polymerises in contact with air, b. is electrically-conductive whilst it is setting, c. consists of polyvinyl alcohol (II), **ethanol** , plasticiser (III) and water, and pref. d. has a viscosity of 2000-3000 pa.s...

...4% aq. soln. at 20 deg.C. (III) may be water soluble lanolin (IV) and **glycerol** (V), in the ratio of 1-4:1. The preferred compsn. (VI) is 20% (II...

...USE/ADVANTAGE - An apparatus contg. (I) corrected to an **electrical generator** for therapeutic or aesthetic facial treatment is claimed. Unlike prior-art processes, professional supervision is...
...Abstract (Equivalent): A conductive **skin** mask to be used in

association with a generator for generating pulsed currents, for the application of such currents to a region of the **skin** of a subject for therapeutic or aesthetic purposes, which is formed by a layer of a composition capable of setting, when spread over the region of **skin** , band being of substantial conductivity in the course of setting, characterised in that the composition is a gel which polymerises in contact with the air, formed by a polyvinyl alcohol, **ethanol** and water ternary mixture, with a plasticiser which is physiologically acceptable on the **skin** , and comprises by weight from 15 to 30% of polyvinyl alcohol with a hydrolysis factor of higher than 85%, from 7 to 15% of **ethanol** and, as plasticiser, from 1.5 to 3% of water-soluble lanolin and from 0.7 to 1.5% of **glycerol** , the balance being water, whereby upon conclusion of polymerisation, application of the currents to the region of the **skin** of the subject comes to an end ...

...Abstract (Equivalent): Disposable conductive cutaneous coating comprises a settable layer spread over the **skin** having electrical conductivity during setting but little when set which comprises a gel progressively polymerisable on contact with air, which is a ternary mixt. of polyvinyl alcohol, **ethanol** and water with acceptable plasticiser. Pref. compsn. is 15-30 (30) % PVA with drg. of hydrolysis above 85%, (7-15) (10)% wt. **ethanol** , 1-5 (2) % by wt. water sol. lanolin 0.7-1.5 (1) % wt. **glycerol** the remainder being water. Viscosity of the gel is adjusted to 2000-3000 PaS. Generator...

...of the cheek bones at ear level. USE/ADVANTAGE - For use on area of persons **skin** when applying electrical currents for therapeutic or beauty treatment. By using a mask of conductivity similar to that of the **skin** and underlying tissues, large locallised voltage gradients and currents are avoided. Gel soln. is stable...

...Title Terms: **SKIN** ;

...International Patent Class (Main): **A61N-001/04**

...International Patent Class (Additional): **A61N-001/30**

29/3,K/10 (Item 10 from file: 350)
DIALOG(R)File 350:Derwent WPIX

007198981
WPI Acc No: 1987-195990/ **198728**
XRAM Acc No: C87-081952
Base composition for iontophoretic **bio-electrode - contains alkyl pyridine- carboxylate**
Patent Assignee: NITTO ELECTRIC IND CO (NITL)
Number of Countries: 001 Number of Patents: 002
Patent Family:

Patent No	Kind	Date	Applicat No	Kind	Date	Week	
JP 62126138	A	19870608	JP 85265787	A	19851126	198728	B
JP 93072890	B	19931013	JP 85265787	A	19851126	199344	

Priority Applications (No Type Date): JP 85265787 A 19851126
Patent Details:

Patent No	Kind	Lan	Pg	Main IPC	Filing Notes
JP 62126138	A		10		
JP 93072890	B		9	A61K-047/16	Based on patent JP 62126138

Base composition for iontophoretic **bio-electrode**...

...Abstract (Basic): Base compsn. for **iontophoretic** bioelectrode is new and contains essential component of formula (I) where R is 6-20C...

...Pref. organic solvents are lower alcohols, cyclic ureas, alkylene glycols, lactam cpds., **glycerin** and **DMSO** .
...

...ADVANTAGE - Any enderic medicines can be applied to the present base. When stuck to **skin** , the pharmaceutical ingredient contained in the base can surely be transferred through the **skin** even under mild electric condition (low voltage and low current) and the bioavailability of the
...Title Terms: **IONTOPHORESIS** ;

```
Set     Items   Description
S1     216513   ENHANC?()AGENT? OR DMSO OR ETHANOL OR PENETRAT?()SOLVENT? -
            OR (SULPHUR? OR SULFUR?)()COMPOUND?()SOLVENT?
S2          0   RN=67-68-5
S3          0   DC=D.02.886.640.150
S4     100516   (CLARIFY? OR CLARIFI?)()AGENT? OR GLUCOSE OR GLUCONIC OR D-
            EXTROGLUCOSE OR DEXTROSE OR DEXTRONIC OR MALTONIC
S5     126731   GLYCOGEN? OR GLYCERYL? OR GLYCERIN? OR GLYCEROL?
S6          0   DC=D09.203.546.359.448
S7          0   RN=50-99-7
S8        106   DIATRIZOATE()MEGLUMINE OR DIATRIZOATE()METHLYGLUCAMINE OR -
            DIATRIZOIC()ACID()METHYLGLUCAMINE OR MEGLUMINE()DIATRIZOATE OR
             METHYLGLUCAMINE()DIATRIZOATE OR (AMIDOTRICOIC OR AMIDOTRIZOI-
            C)()ACID? OR MEGLUMINE()AMIDOTRIZOATE
S9          0   RN=131-49-7
S10         0   DC=(D02.033.800.813.550.500 OR D02.241.223.100.140.100.375-
            .880.275 OR D09.203.037.342.600.500 OR D09.203.853.813.550.50-
            0)
S11     27583   IONTOPHORE? OR IONTOTHERAP? OR IONIC()THERAP? OR EMDA OR S-
            ONOPHORE? OR ELECTROPORAT? OR ELECTRO()PORAT?
S12         0   DC=E05.300.650
S13        86   (MICRONEEDLE? OR MICRO()NEEDLE?)()ARRAY? ?
S14    923704   INCREAS? OR ENHANC? OR AMELIORAT?
S15    910277   PERMIT? OR PERMISS? OR ALLOW?
S16    808104   BETTER? OR IMPROV?
S17     84730   RECEPTABIL? OR PERMEABIL? OR PERMEABL? OR LUCENCY?
S18    240168   TRANSLUCEN? OR TRANSPAREN? OR CLEARNESS OR CLARITY
S19    579082   OPTICAL? OR LIGHT? OR LUCID?
S20    109002   PERMEAB?()(BARRIER? OR LAYER? OR STRAT?) OR SKIN
S21     40240   CONJUNCTIV? OR EPITHELI? OR SCLERA? OR STRAT?()CORNE? OR (-
            INTERSTIT? OR INTER()STIT?)()(SPACE? OR TISSUE?)
S22     88098   IC=(A61N? OR A61M? OR A61B?)
S23     17869   DIMETHYL()(SULFOXIDE OR SULPHONYL) OR DIMEXIDE OR RIMSO OR
            RIMSO100 OR SULFINYL()BISMETHANE OR SULFINYLBISMETHANE
S24     71850   (DRIVING OR ELECTRIC()PULSE OR ELECTRICPULSE OR ELECTROMOT-
            IVE OR ELECTRO()MOTIVE OR ACOUSTIC? OR ULTRASONIC? OR ELECTRI-
            CAL? OR RADIOFREQUENCY? OR RADIO()FREQUENCY OR TEMPERATURE OR
            THERMAL OR PHYSICAL OR CHEMICAL OR CONCENTRATION OR E...
S25     19899   (S1:S3 OR S23) AND S4:S10 AND (S11:S13 OR S24)
S26     11065   S25 AND S20:S21
S27      9684   S26 AND S14:S16 AND S17:S19
S28      2448   S27 AND S14:S16(5N)S17:S19
S29        54   S28 AND (S1:S3 OR S23)(5N)S20:S21 AND S4:S10(5N)S20:S21
S30         6   S29 AND S22
S31        54   S29:S30
S32         7   S31 AND PY<1999
S33         7   IDPAT (sorted in duplicate/non-duplicate order)
? show files
File 348:EUROPEAN PATENTS 1978-2003/Nov W04
         (c) 2003 European Patent Office
File 349:PCT FULLTEXT 1979-2002/UB=20031203,UT=20031127
         (c) 2003 WIPO/Univentio
```

33/5,K/2 (Item 2 from file: 348)
DIALOG(R)File 348:EUROPEAN PATENTS

00786612
FORMULATIONS AND METHODS FOR REDUCING SKIN IRRITATION
FORMULIERUNGEN UND VERFAHREN ZUR VERMINDERUNG VON HAUTIRRITATIONEN
FORMULATIONS ET PROCEDES POUR DIMINUER L'IRRITATION DE LA PEAU

PATENT ASSIGNEE:
COSMEDERM TECHNOLOGIES, (2168921), 4370 La Jolla Village Drive, Suite 960 , San Diego, CA 92122, (US), (Proprietor designated states: all)
INVENTOR:
HAHN, Gary, Scott, 2371 Lagoon View Drive, Cardiff by the Sea, CA 92007, (US)
THUESON, David, Orel, 12740 Boxwood Court, Poway, CA 92064, (US)
LEGAL REPRESENTATIVE:
Warcoin, Jacques (19071), Cabinet Regimbeau 20, rue de Chazelles, 75847 Paris cedex 17, (FR)

PATENT (CC, No, Kind, Date): EP 801554 A1 971022 (Basic)
EP 801554 B1 030416
WO 96019183 960627
APPLICATION (CC, No, Date): EP 95943956 951221; WO 95US16765 951221
PRIORITY (CC, No, Date): US 362058 941221
DESIGNATED STATES: AT; BE; CH; DE; DK; ES; FR; GB; GR; IE; IT; LI; LU; MC; NL; PT; SE
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Assignee: 030402 A1 Transfer of rights to new applicant: COSMEDERM TECHNOLOGIES (2168921) 4370 La Jolla Village Drive, Suite 960 San Diego, CA 92122 US
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FORMULATIONS AND METHODS FOR REDUCING SKIN **IRRITATION**

...SPECIFICATION This invention relates to compositions and formulations, and methods for using the same, to inhibit **skin** irritation in animals.

Background

Many substances are applied topically to the **skin** or mucous membranes of humans or animals (hereafter " **skin** ") in order to alter the subject's appearance, to protect the subject from the environment, or to produce a biological change in the **skin** or other tissue for therapeutic, preventive or cosmetic purposes. These substances may generically be termed...

...liquids such as sprays or mists. Examples of topical products commonly classified as "cosmetics" include **skin** care products such as creams, lotions, moisturizers and "treatment cosmetics" such as exfoliants and/or **skin** cell renewal agents; fragrances such as perfumes and colognes, and deodorants; shaving-related products such as creams, "bracers" and aftershaves; depilatories and other hair removal products; **skin** cleansers, toners and astringents; premoistened wipes and washcloths; tanning lotions; bath products such as oils...

...such as eye lotions and makeup removers; foot care products such as powders and sprays; **skin** colorant and make-up products such as foundations, blushes, rouges, eye shadows and liners, lip...

...lotions, oils, shampoos, powders and wet wipes; feminine hygiene products such as deodorants and douches; **skin** or facial peels applied by dermatologists or cosmeticians; and others. Examples of topical products commonly...

...Other topical products include hand, facial and body soaps and detergents and other forms of **skin** cleansers, as well as household detergents and many other household products such as solvents, propellants...

...chemicals which may produce "irritation," including various inflammation symptoms or signs, when applied to the **skin** or mucosa (" **skin** "). The present invention is directed in part to compositions and methods for inhibiting the irritation...

...or edema (swelling). The irritation response may be due to the direct effect on the **skin** of certain topical product chemicals or to a response by the immune system directed toward the chemicals alone or in combination with **skin** components (e.g. antigens).

The sensation of itch is one of the most common **skin** problems experienced by humans and animals. Itch can be defined as a sensation which provokes the desire to scratch the site from which the sensation originates. All **skin** contains sensory nerves which can transmit itch or other sensory impulses in response to chemical...

...Bernhard. McGraw-Hill, Inc. (San Francisco, 1994), pp. 1-22. The sensory nerves of the **skin** can be considered to be a "final common pathway" for the many irritating conditions which...

...sensed as itch including chemical exposure, environmental exposure (such as that which produces dry, itchy **skin**) and disease processes such as atopic dermatitis. Many chemical substances are able to produce itch or other sensory impulses when topically applied to the **skin** , No matter what the ultimate cause of itch, the sensation experienced is the same

and...

...in topical products are known irritants or are potentially irritating, especially to people with "sensitive **skin** ". These irritating ingredients include fragrances, preservatives, solvents, propellants and many other ingredients that might otherwise...

...including chemicals that may also be classified as drugs, produce irritation when applied to the **skin** . These include, but are not limited to, such ingredients as exfoliants and **skin** cell renewal agents, anti-acne drugs, antiperspirant compounds, antihistamines, anti-inflammatory agents, **skin** protective agents, insect repellent chemicals, sunscreens and many others. Where more than one chemical irritant...

...additive. Furthermore, chemical ingredients may react with one another, or in the environment of the **skin** , to form new chemicals which are irritating. The vehicles in which the active drug ingredients...

...the case of drugs such as topical corticosteroids.

In addition to chemicals which directly trigger **skin** irritation, some chemicals indirectly cause the **skin** to become ...chemicals or environmental conditions which would not normally cause irritation. Many chemicals which act as **skin** "exfoliants" such as retinoids (e.g. tretinoin, retinol and retinal), carboxylic acids including (alpha)-hydroxy...

...octanoic acid, gluconolactone, methoxypropyl gluconamide, oxalic acid, malic acid, tartaric acid, mandelic acid, benzylic acid, **gluconic** acid, benzoyl peroxide and phenol, among others, may cause the **skin** to become more sensitive to irritation triggered by other topically-applied chemicals such as moisturizers...

...e.g. soaps, shaving cream) and other topical products. Exfoliants and other ingredients may also **increase** the **skin** 's sensitivity to environmental conditions such as sunlight, wind, cold temperature and dry air, or...

...chemical agents such as antigens, or may exacerbate the irritation attributable to a pre-existing **skin** disease.

Conversely, environmental influences may themselves **increase** the **skin** 's sensitivity to chemicals in topical products by reducing the epidermal **skin** 's "barrier function." The barrier function acts to minimize absorption or passage of potentially irritating chemicals through the outer "dead" cell layer of epidermal **skin** into the living **skin** tissue. Extremes of humidity, for example, can greatly **increase** irritation from topically-applied products. A very common condition due to low humidity is termed...

...heating) or long exposure to refrigerated air from air conditioners in the summer produces itchy **skin** -- especially in older people -- which can exacerbate the irritating effects of topical products. Additionally, soaps, detergents, cleansing products, shaving creams, alcohol and other products which remove some of the **skin** 's protective lipids and/or secretions may **increase** the **skin** 's **permeability** and sensitivity to topically-applied chemicals which would otherwise not produce irritation. Normal processes such as sweating may also **increase** the ability of irritant materials, such as antiperspirants, deodorants or sunscreens, to penetrate the **skin** through pores or glands, thus exacerbating the potential for irritation. Exposure of the **skin** to high humidity

environments or liquids may also **increase** the ability of potential irritants to penetrate the **skin** . Similarly, the **skin** may become sensitized or inflamed due to infection, shaving abrasion, repeated or excessive washing or...

...deodorants, after-shaves or other topical products.

In addition to chemical and environmental causes of **skin** irritation, many people have an inherent sensitivity or genetic predisposition to **skin** irritants. People with respiratory allergies, for example, tend to have excessively dry **skin** which facilitates **increased** absorption of potentially irritating chemicals. The excessively dry **skin** which accompanies atopic dermatitis, for example, predisposes patients with this condition to irritation from many topically-applied products. Other **skin** diseases and conditions such as allergic or non-allergic contact dermatitis, asthma (including exercise-induced asthma as may be precipitated by inhalation of cold or dry air), rhinitis, **conjunctivitis** , inflammatory bowel disease, psoriasis, eczema, post-herpetic neuralgia, infectious diseases manifested by, for example, sore throat or **skin** lesions such as candidiasis, insect bites and the like produce inherent irritation which may be...

...such as antigens, cold air, low humidity and the like. Many other individuals exhibit sensitive **skin** as a condition that is not related to an identifiable **skin** disease.

Whatever the exact cause of irritation, many attempts have been made to reduce the...

...like to designate a product's reduced tendency to cause irritation in consumers with sensitive **skin** . Many **skin** (including mucosal) irritation responses, however, are not allergic in origin. In any event, it is...

...there is a substantial practical and commercial need in the field of exfoliants and related **skin** care products for a composition or method that will reduce or prevent the irritation caused...

...octanoic acid, gluconolactone, methoxypropyl gluconamide, oxalic acid, malic acid, tartaric acid, mandelic acid, benzylic acid, **gluconic** acid, peroxides, phenols, and **skin** cell renewal agents such as retinoids. Such products are used as exfoliants and/or cell renewal agents to reduce the occurrence or severity of **skin** wrinkles, particularly facial wrinkles, or as anti-acne, anti-"dry **skin** " or **skin** whitening agents. See U.S. Patent Nos. 4,105,782, 4,105,783, 4,246...

...et al.) and 5,262,153 (Mishima et al.); W.P. Smith, "Hydroxy Acids and **Skin** Aging," Soap/Cosmetics/Chemical Specialties for September 1993, p. 54 (1993). Hydroxy acids, in concentrations high enough to exfoliate, are well known often to cause **skin** irritation and rashes. The danger of irritation is even higher for persons that have sensitive **skin** .

Currently available methods reported by Yu et al. to reduce the irritation caused by hydroxy...reported drawback of reducing the ability of the resulting hydroxy acid salt to penetrate the **skin** and thus compromising the beneficial effects (particularly anti-acne or anti-"dry **skin** " effects) of the hydroxy acid. Alternatively, Yu et al. have proposed the approach of formulating...

...is, again, to raise the pH of preparation to a non-irritating level. However, the **increased** pH (reduced acidity) of the resulting preparations renders them less efficacious as exfoliating or anti...

...reported that certain alkali or alkaline-earth metal salts of lactic acid were useful as **skin** -whitening agents (U.S. Pat. No. 5,262,153), but no recognition is expressed as...

...of Mishima were typically "neutralized" or adjusted to pH 5.5 prior to screening or **skin** -whitening testing (see Experiments I and 2). A clear need exists, therefore, for a composition or method that prevents or reduces the **skin** irritation caused by low-pH (high-acidity) organic or inorganic acid products but that does...

...otherwise safe and effective topical products, or to reduce the intrinsic irritation associated with various **skin** diseases and conditions (such as atopic or other dermatitis, asthma (including exercise-induced asthma), rhinitis or other respiratory inflammation, **conjunctivitis** , inflammatory bowel disease, eczema or psoriasis) or caused by exposure to irritating chemicals or environmental...

...of the invention are useful in reducing the incidence and severity of irritation associated with **skin** exposure to irritating chemicals or environmental conditions. While the exact mechanism (or mechanisms) of activity...

...is presently believed that the cations of the invention may reduce irritation by interacting with **skin** nerve cells to prevent or counteract the sensation of irritation, and/or by interfering with irritation-inducing components of **skin** cells that are triggered by application of or exposure to the irritant. Thus, the cations may alter the ability of **skin** nerve cells to depolarize or repolarize, as for example by blocking or interfering with ion...

...or alternatively, the cations ofthe invention may act to inhibit or modify the action of **skin** cell proteases or other irritation-inducing biological molecules (such as eicosanoids or cytokines) that may otherwise be activated by topical application of **skin** irritants, or may alter "second-messenger" function within sensory cells.

A number of ionic species...form of stannous chloride as an ingredient to provide fast-acting, efficient and safe topical **skin** anti-irritant effects, and to formulations containing such selected cations. It is one object of the present invention to provide ingredients, formulations and methods of use which can suppress **skin** irritation due to chemical or environmental exposure, or due to tissue inflammation, injury or other **skin** pathology. The invention is particularly useful for preventing, reducing or eliminating the potential irritation caused...

...meets a clear need for formulations and ingredients that will prevent or reduce the potential **skin** irritation caused by topical products. The invention is also useful for preventing, reducing or eliminating the **skin** irritation caused by **skin** diseases or other conditions such as environmental exposure to irritating chemicals or influences such as...

...acidity or basicity in the formulated composition, and a total cation concentration effective to reduce **skin** irritation. In one such particularly preferred embodiment, a cation of the present invention is combined...

...terms, but that such acidity will manifest itself upon exposure of the formulation to the **skin** where water is present both intracellularly and extracellularly.

In another embodiment, the cation of the...

...362,100, 08/362,097, and 08/362,055 (entitled "Formulations and Methods

for Reducing **Skin** Irritation" and published in Europe under EP 0 796 078 and EP 0 799 018...

...a multiple anti-irritant effect.

The invention further provides methods of treating, reducing or eliminating **skin** irritation comprising the topical application of a formulation comprising an anti-irritant effective amount of...

...development of irritation or to treat a pre-existing irritation attributable to conditions such as **skin** disease, chemical irritant exposure or environmental exposure.

Description of the Drawings

FIGURES 1 through 4...

...panel of humans treated with 250 mM stannous chloride (and control) in a lactic acid **skin** irritation challenge.

FIGURE 5 depicts experimental data showing the cumulative irritation inhibition effects of aluminum chloride administered at varying concentrations (31-500 mM) in a lactic acid **skin** irritation challenge.

FIGURE 6 depicts experimental data showing the cumulative irritation inhibition effects of stannous chloride administered at varying concentrations (31-500 mM) in a lactic acid **skin** irritation challenge.

Detailed Description

Human clinical trials undertaken in connection with the present invention have established that the cation species tin(II) (Sn^{2+}) is effective, when applied topically to the **skin** in appropriate concentrations and vehicles, to suppress the relatively severe stinging, burning, tingling, itching and/or erythema induced by topical application of the hydroxy acid **skin** irritant lactic acid. Formulations containing such cation are useful in suppressing a wide range of...For example, the cation of the present invention is useful for preventing or reducing the **skin** irritation caused by (alpha)- or (beta)-hydroxy acids, (alpha)-keto acids and other carboxylic acids...

...acid, gluconolactone, methoxypropyl gluconamide, oxalic acid, malic acid, tartaric acid, mandelic acid, benzylic acid, and **gluconic** acid), as well as in certain prescription topical drugs containing high (for example, 12% w...

...inhibited by the formulations of the invention. Additionally, formulations containing such cations are useful in **ameliorating** irritation in conditions where the **skin** is inherently hypersensitive to topical products (e.g. dry **skin** , "winter itch," and other inflammation or injury conditions) and in **ameliorating** the irritation due to such conditions even in the absence of other applied topical products. The formulations are also useful in treating non-human animal **skin** irritation, as for example dog or cat irritation and resultant scratching due to fleas or other **skin** disease or condition.

An additional benefit of the present anti-irritant compounds and formulations is...

...they do not have the undesirable anesthetic side-effects exhibited by Lidocaine and other similar **skin** local anesthetics. Upon application of a solution of the compound used in the clinical trials...

...of the invention comprise a topical vehicle suitable for administration to the animal (particularly human) **skin** , and an amount of cation of the invention effective to reduce, inhibit or eliminate existing or potential **skin** irritation. The cation is accompanied in the formulation by

chloride counterions, although the cation-anion...

...irritant topical formulations additionally contain an irritant ingredient(s) that is itself capable of inducing **skin** irritation such as symptoms associated with inflammation, as for example a cosmetic or **skin** care product ingredient, or a pharmaceutically active ingredient or drug ingredient.
The cation for use...

...in a topical formulation in a concentration effective to prevent or reduce (hereafter, "inhibit") the **skin** irritation (such as inflammation) symptoms that are sought to be eliminated. The formulation contains such...
...0.5 grams of cation formulation over a 5 cm x 5 cm area of **skin** (25 cm2)). Clinical studies have shown that such preferred concentration ranges are generally effective to inhibit **skin** irritation and, in typical topical vehicles, are readily formulated and do not leave any significant visible residue when applied to the **skin** . Higher concentration formulations, such as saturated pastes or other forms, may also be successfully used...

...adjusted to account for the amount of formulation that is typically applied to a given **skin** area by the user, which will depend to an extent on the physical nature of...

...amount of cation required may be reduced in such cases where the formulation contains a **skin** penetration- **enhancing** ingredient or other agent which **increases** the ability of the cations to permeate the **stratum corneum** to their site of anti-irritant activity. Preferably, the formulations of the invention include an...362,100, 08/362,097, and 08/362,055 (entitled "Formulations and Methods for Reducing **Skin** Irritation"), filed December 21, 1994). Other anti-irritant agents, such as steroids or non-steroidal...

...is preferred that the selected salt be sufficiently soluble in the formulation vehicle as to **allow** a consistent formulation having the desired physical and topical application characteristics. It will be recognized...

...preferred that the salt chosen be sufficiently aqueous-soluble such that, upon application to the **skin** , the component cation (and corresponding counteranion) can dissociate and be taken up into the water-containing milieu of the **skin** . In addition, it will be clear that the particular salt ingredient chosen should be topically...

...exhibit higher solubility in many common topical vehicles and suitable ionization upon application to the **skin** . In addition, strongly acidic anion components may be useful where it is desired to maintain...

...water; organic solvents such as alcohols (particularly lower alcohols readily capable of evaporating from the **skin** such as **ethanol**), glycols (such as **glycerin**), aliphatic alcohols (such as lanolin); mixtures of water and organic solvents (such as water and alcohol), and mixtures of organic solvents such as alcohol and **glycerin** (optionally also with water); lipid-based materials such as fatty acids, **acylglycerols** (including oils, such as mineral oil, and fats of natural or synthetic origin), phosphoglycerides, sphingolipids...
...emulsifying agents; and other vehicles and vehicle components that are suitable for administration to the **skin** , as well as mixtures of topical vehicle components as identified above or otherwise known to the art. The

vehicle may further include components adapted to **improve** the stability or effectiveness of the applied formulation, such as preservatives, antioxidants, **skin** penetration **enhancers** , sustained release materials, and the like. Examples of such vehicles and vehicle components are well...the formulation -- such as a treated or premoistened bandage, wipe, washcloth or stick -- to the **skin**); spraying (including mist. aerosol or foam spraying); dropper application (as for example with ear or...

...a suitable powder form of the formulation); soaking; and injection (particularly intradermal or subcutaneous injection). **Iontophoresis** or other electromagnetic- **enhanced** delivery systems may also be usefully employed, as for example to **increase** delivery to the dermis.

Methodologies and materials for preparing formulations in a variety of forms...

...products); Chapter 14, pp. 325-380 (hand products); Chapter 15, pp. 381-460 (body and **skin** creams and lotions); and Chapter 16, pp. 461-484 (baby products).

The formulations of the...

...as occurring with any accompanying anion counterion components) is substantially invisible upon application to the **skin** . This is particularly true in the case of many cosmetic formulations that are applied to...

...of the body. It will be recognized that in some cases, particularly with colored facial **skin** care products such as blushes, blemish covers, lipsticks and the like, the formulation will be designed to be visible on the **skin** ; in such cases, it is desirable that the cation component itself be "invisible," that is, that it not adversely change the appearance of the overall formulation as applied to the **skin** .

In another embodiment of the invention, the present cation can be formulated in a form...

...determine whether and to what extent the cations of the present invention reduced or prevented **skin** irritation caused by lactic acid, an (alpha)-hydroxy carboxylic acid known for its **skin** irritating potential. The trials were conducted in a double blind, randomized, vehicle-controlled manner. Various...

...with Ivory bar soap in the clinic prior to application of test solutions.

Lactic acid **skin** -irritant compositions were formulated in an appropriate vehicle prior to application to the **skin** of the subjects. In the majority of the tests, the irritant composition was 7.5% lactic acid dissolved in a 10% **ethanol** -in-water solution. In the case of stannous chloride, which is not appreciably soluble in 10% **ethanol** , a water- **ethanol** - **glycerin** solution was used (composition 33.75% water, 33.75% **glycerin** ("Gly"), 25% **ethanol** , with 7.5% lactic acid). Test anti-irritant formulations were prepared by combining measured amounts...

...irritant composition. The test formulation was applied to a defined portion of the subject's **skin** , typically the face. Controls were performed by applying ...with an equimolar amount of sodium chloride to a contralateral portion of the subject's **skin** .

All test solutions (including controls) were applied in a double blind, randomized fashion using the...

...the left.

Sensory assessment scores were recorded for each treated side of the

subject's **skin** every minute for 15 minutes or until three consecutive scores of "zero" irritation were obtained...

...sensations represented by a score of I to be an indication that a facial treatment **skin** care product (especially an exfoliant) was working as advertised. By contrast, irritation scores of "2...

...likely often result in a consumer never purchasing the product again. In those subjects and **skin** samples where an irritation was sensed, the irritation commonly involved a spectrum of burn-sting...

...shows the time course of irritation responses for both cation-treated and non-treated (control) **skin** portions for the panel. FIG. 2 shows the cumulative irritation over time for the same...

...Toner (an alcohol-containing solution). The concentrations achieved were shown to be effective to inhibit **skin** irritation.

...CLAIMS B1

1. A composition for inhibiting **skin** irritation in an animal subject comprising an anti-irritant amount of from 250 mM to...

...subject comprising a topical vehicle;

an irritant ingredient contained in an amount capable of inducing **skin** irritation in said subject; and

an anti-irritant amount of from 250 mM to 500...

...product.

4. The composition of any of the foregoing claims wherein said composition comprises a **skin** exfoliant, **skin** peel or **skin** cell renewal agent
5. The composition of any of the claims 2 to 4 wherein...

...octanoic acid, gluconolactone, methoxypropyl gluconamide, oxalic acid, malic acid, tartaric acid, mandelic acid, benzylic acid, **gluconic**0 acid, pyruvic acid and phenol.

7. The composition of any of the foregoing claims wherein...

...the concentration range of stannous chloride is from 50mM to 2000mM for the treatment of **skin** irritation attributable to a pre-existing human **skin** disease or **skin** irritation condition, including preferably **skin** irritation attributable to atopic dermatitis, non-atopic dermatitis, asthma, rhinitis, **conjunctivitis** , eczema, psoriasis or infectious disease; environmental exposure to one or more of sunlight, low humidity...

...selected from the group consisting of antiperspirant, deodorant, sunscreen, tanning, sunburn treatment, insect repellant, exfoliant, **skin** peel, **skin** cell renewal, fragrance, shaving or hair removal, hair care or hair treatment, cleanser, astringent, toner...

...topical drug products; insect sting or bite, or plant exposure; one or more of shaving, **skin** cleansing or bathing, sweating and physical **skin** trauma; and dry **skin** .

13. The use of stannous chloride for the manufacture of a topical medicament wherein the...

...range of stannous chloride is from 50mM to 2000mM for the treatment or inhibition of **skin** irritation attributable to an irritant ingredient contained in said composition.

14. The use of stannous chloride according to any of the claims 12 or 13 wherein said **skin** irritation is selected from the group consisting of ocular irritation, respiratory system irritation, gastrointestinal system irritation, reproductive system irritation, irritation of a mucous membrane, irritation of epidermal **skin** , and irritation of dermal **skin** .
15. The use of stannous chloride according to any of claims 12 to 14, wherein said topical composition comprises an amount of said cation capable of inhibiting said **skin** irritation in subjects experiencing the same by an average of at least 20 %.
16. The capable of inhibiting said **skin** irritation by at least 40 % in at least 10 % of the subjects experiencing the same...

...wherein said topical composition comprises an amount of said cation capable of Inhibiting mean cumulative **skin** irritation in a susceptible human population, wherein said inhibition of **skin** irritation represents an average reduction in one or more of sting, bum and itch in...

...or following administration of said topical product.
20. A cosmetic method comprising applying to the **skin** the composition of any of claims 1 to 11, wherein said composition is a cosmetic...
...CLAIMS zuschreibbar ist, einschlieslich vorzugsweise einer Hautreizung, die einer atopischen Dermatitis, nicht-atopischen Dermatitis, Asthma, Rhinitis, **Conjunctivitis** , Ekzem, Psoriasis oder infektioser Erkrankung; Umgebungseinwirkung von Sonnenlicht, geringer Feuchtigkeit, Wind, kalter Temperatur und/oder...

33/5,K/3 (Item 3 from file: 348)
DIALOG(R)File 348:EUROPEAN PATENTS

00368836
The use of asymetric membranes in delivery devices.
Verwendung von asymmetrischen Membranen in Abgabevorrichtungen.
Utilisation de membranes asymetriques en dispositifs de liberation.
PATENT ASSIGNEE:
PFIZER INC., (200961), 235 East 42nd Street, New York, N.Y. 10017, (US),
(applicant designated states: AT;BE;CH;DE;ES;FR;GB;GR;IT;LI;LU;NL;SE)
INVENTOR:
Cardinal, John Robert, 37 Coult Lane, Old Lyme Connecticut, (US)
Herbig, Scott Max, Rimrock West No. 6, Bend Oregon, (US)
Korsmeyer, Richard Wilker, 10 Green Valley Lakes, East Lyme Connecticut, (US)
Lo, Jeelin, 20 Old Stagecoach Road, Old Lyme Connecticut, (US)
Smith, Kelly Lincoln, 19295 Dayton Road, Bend Oregon, (US)
Thombre, Avinash Goviind, 3 Little John Court, Gales Ferry Connecticut, (US)
LEGAL REPRESENTATIVE:
Wilkinson, Stephen John et al (52061), Stevens, Hewlett & Perkins 1 St. Augustine's Place, Bristol BS1 4UD, (GB)
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CITED PATENTS (EP A): US 4837111 A; EP 171457 A; US 4687660 A; EP 56825 A
CITED REFERENCES (EP A):
Desalination vol. 35, 1980, Amsterdam, Netherlands pages 39 - 58; H. Strathmann: "Development of new membranes";

ABSTRACT EP 357369 A2
A device for controlled release of an active substance through one or more asymmetric membranes by diffusion and/or osmotic pumping.
ABSTRACT WORD COUNT: 24

LEGAL STATUS (Type, Pub Date, Kind, Text):

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CLAIMS B	(English)	EPBBF1	3095
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CLAIMS B	(French)	EPBBF1	2042
SPEC B	(English)	EPBBF1	20010
Total word count - document A			0
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...SPECIFICATION B1

Asymmetric membranes, which consist of a very thin, dense **skin** supported by a thicker, porous substructure layer, **are** used extensively in the reverse-osmosis desalination of brine. The technology for the formation of...

...developed by Loeb and Sourirajan (Adv. Chem. Ser. 38, 117 (1962)) and continues to be **improved** .

Asymmetric membranes of polyquinoxalines have been employed **in** the separation of gaseous mixtures (U.S. Patent 4,732,586).

While the literature is...

...is feasible and practical.

A preferred feature of the device is a membrane which is **permeable** and imperforate and where the release is **either** substantially by osmotic pumping or substantially by diffusion.

A second preferred feature of the device is a membrane which is **permeable** and perforate and where the release is **either** substantially osmotic pumping or substantially by diffusion.

A third preferred feature is a device in...

...the amount of 15% by weight and the pore-forming substances are formamide, acetic acid, **glycerol** , a (C(sub 1)-C(sub **4**))alkanol, sodium acetate, aqueous hydrogen peroxide or polyvinylpyrrolidone. Especially preferred is the use of **ethanol** as a pore-forming agent, present **in** the amount of 30% by weight or the use of **glycerol** as a pore-forming agent, present **in** the amount of 10% by weight.

A second preferred wet process for preparing tablets comprises...

...the amount of 15% by weight and the pore-forming substances are formamide, acetic acid, **glycerol** , a (C(sub 1)- **C** (sub 4))alkanol, sodium acetate, aqueous hydrogen peroxide or polyvinylpyrrolidone. Especially preferred is the use of **ethanol** , as a pore-forming **agent** , present in the amount of 30% by weight.

Another preferred phase inversion process for preparing comprised of **glycerol** , water, **butanol** and **ethanol** present **in** the amount of 1.9, 2.7, 11.7 and 21.7%, respectively, by weight...

...the amount of 16% by weight and the pore-forming substance is formamide, acetic acid, **glycerol** , a (C(sub 1)-C(sub 4))alkanol, sodium acetate, aqueous hydrogen peroxide or polyvinylpyrrolidone. Especially preferred is the use of **ethanol** and **glycerol** as pore-forming substances, present in the amount of 28 and 8%, respectively, by weight. Also especially preferred is the use of **glycerol** as the pore-forming substance, present in the amount of 10% by weight.

Also part...

...by using cyclones.

Preferred within this process is the use of a pore-forming mixture **comprising** 38% by weight **of** the total and composed of **ethanol** , butanol, water and **glycerol** present in the amount of 57, 31, 7 and 5%, respectively, by weight, and the...

...beads after the membrane has solidified and drying.

Preferred in this process is the use **of** cellulose acetate 398-10 present in the amount of 15% and the pore-forming substance is **ethanol** present in the amount of 33% by weight.

Preferred in this method is a device...

...is a tablet, capsule or bead. Especially preferred is said device wherein the membrane is **permeable** and imperforate or perforate, and the

release is substantially either by diffusion or osmotic pumping. Also especially preferred is **said** device wherein the membrane is semipermeable and imperforate and the release is substantially osmotic pumping...

...comprised of one or more asymmetric membranes. Preferred is said device wherein the membrane is **permeable** and perforate or imperforate. Especially preferred is such a device wherein the release is by osmotic pumping.

Finally, the **instant** invention relates to a process for preparing a capsule shell to be used for controlled...

...the amount of 16% by weight and the pore-forming substance is formamide, acetic acid, **glycerol** , a (C(sub 1)-C(sub 4))alkanol, sodium acetate, aqueous hydrogen peroxide or polyvinylpyrrolidone. Especially preferred **is** the use of **ethanol** and **glycerol** as pore-forming substances, present in the amount of 28 and 8%, respectively, by weight. **Also** especially **preferred** is the use of **glycerol** as the pore-forming substance, present in the amount of 10% by weight.

The present invention also **relates** to a process for preparing a bead, tablet or capsule device for controlled release of ...the desired number of asymmetric membranes have been applied. Especially preferred is the use of **ethanol** as the pore-former and cellulose acetate 398-10 as the membrane material.

The present **invention** also includes a process for preparing a tablet for controlled release of one or more...

...by weight in acetone. Especially preferred is the use of cellulose acetate 398-10 and **glycerol** , water, butanol and **ethanol** together as pore-formers in the amount of 2, **2** .8, 12.4 **and** 22% by weight, respectively.

Figure 1 shows the SEM (scanning electron microscope) cross section of an asymmetric membrane tablet coating having a dense imperforate **skin** prior to use. The membrane was prepared according to the procedure of Example **1** , employing a phase inversion-wet process and using cellulose acetate as the membrane material and...

...shows the SEM cross section of an asymmetric membrane tablet coating having an imperforate dense **skin** . The table membrane was prepared according to the procedure of Example 2, utilizing **a** phase inversion wet process wherein the coated tablet was immersed in an aqueous quench bath...

...coated tablet.

Figures 8, 9, 10 and 11 are SEM which show the effects of **increasing** amounts of the pore-forming substance **glycerol** on the size of holes or **ports** in the dense membrane of an **asymmetric** membrane coated tablet, prepared in Example 11.

Figure 12 shows the SEM of dense **skin** of an asymmetric membrane coated tablet prepared by a wet phase inversion process, **as** described in Example 12, where sodium acetate was employed as a pore-forming substance.

Figure...

...outer surface and cross section of a capsule made of an asymmetric membrane in which **glycerol** was employed as the pore-forming substance.

Figure 16 shows an SEM of **the** surface and cross section of a bead covered with an asymmetric membrane and made by...

...an asymmetric membrane layer, prepared as described in Example 21. Note that only one dense **skin** is visible.

Figure 18 shows the release rate of doxazosin from asymmetric membrane **coated** beads having from one to three coats of an asymmetric membrane.

Figure 19 depicts the...in nature. This substructure supports the other portion of the membrane, a very dense, thin **skin** .

The materials of which the asymmetric membranes of the present invention are made **consist** of cellulose derivatives. In particular, they consist of cellulose esters and ethers, namely, the mono process can also use a pore-forming substance or substances to **enhance** the porous nature of the substructure of the membrane. These pore-forming substances **are** , generally, poor solvents for the polymer and are usually dissolved out in the quench bath...

...solution of polymer and pore-forming substance; however, in the dry process the solvent is **allowed** to evaporate completely. The successful formation of an asymmetric membrane using the dry **process** requires that the solvent or solvents evaporate more rapidly than the pore-forming substance. In...

...membrane. The porous channels in the substructure of the polymer can extend through the dense **skin** , resulting in macropores or a series of holes on the exterior **skin** of **the** device. Thus, by **increasing** the pore-forming substance it is possible **to** progress from a device having **a** porous substructure and an imperforate **skin** to one having a highly perforate **skin** (Figures 8, 9, 10 and 11 - **Example** 11).

Pore-forming substances in the **wet** process include formamide, acetic acid, **glycerol** , an alkanol of one to four carbon atoms, 10% aqueous hydrogen peroxide and **polyvinyl**pyrrolidone or combinations thereof. Sodium acetate, or other inorganic salts, can be employed as pore-forming ...

...polymer when the quench is an aqueous quench, leaving macropores in the dense membrane or **skin** . Suitable pore-forming substances for the dry process include **glycerol** , water, alkanols, oils, **surfactants** , glycols or combinations thereof. Rapid drops in pressure during **the** precipitation of the polymer can also result in **enhanced** macropore formation when the dry process is employed. For example, spray drying beads **coated** with a polymer solution under pressure into a chamber at a lower pressure can result...

...required to give the desired asymmetric membrane.

Asymmetric-membrane coatings with macropores through the outer **skin** (perforate membrane coatings) can also be made by adjusting the quench-bath conditions. **Raising** the temperature of the quench bath to temperatures near the boiling point of the solvent...

...macropore formation upon precipitation of the polymer in the quench bath. Other nonsolvents, such as **ethanol** , can be added to the quench bath to cause macropores to form in **the** membrane coatings. Thus, either perforate or imperforate membranes can be formed depending on the quench-bath temperature and composition.

Asymmetric-membrane coatings that have macropores through the outer **skin** can also be made by making membrane coatings using two or more incompatible **polymers** . The quantity of macropores through the surface an be a controlled by the relative concentrations...

...24 - Example 29).

Macropores can also develop in situ by the rupturing of the dense **skin** located directly over a channel in the substructure. Thus, an imperforate membrane becomes **perforate** during use.

The active substances and excipients are released from the device of

the present...

...osmotically effective compounds in the core of the device. These osmotically effective compounds are the **driving force** of the device and provide a higher osmotic pressure inside the device **than that** of the exterior environment, which in the case of a medicinal agent being given orally...

...When the device of this invention is intended for human or veterinary use, the osmotic **enhancing agents** should be pharmaceutically acceptable.

Other excipients present in the devices of this **invention include** such water soluble binders as polyethylene glycol, gelatin, agar carboxycellulose, ethylmethylcellulose, polyvinyl alcohol, water soluble ...methods for releasing active substances from the core of said device, the membrane can be **permeable** , meaning that both solvent and active material can pass through the membrane, and **imperforate** , meaning there are no visible macropores in the dense thin **skin** . If the **skin** is sufficiently strong or the osmotic core pressure sufficiently low, **the** release from **this** device may be substantially by diffusion (the term "substantially" implies that most, i.e., over 50% of the release is by this release mechanism). If the thin **skin** forms macropores in situ, the device would continue to release by diffusion. If **the** core of the device contains osmotically effective compounds or substances, the osmotic pressure could rupture the **skin** over the channels of the substructure and the release will be substantially by **osmotic** pumping.

The membrane can also be **permeable** and perforate. The delivery or release without osmotic substances will be substantially by **diffusion** unless the active substance itself is osmotically active. With osmotic **enhancing** substances in the core of the device the release can be substantially osmotic **pumping** .

The membrane can also be semipermeable, meaning that only the solvent can pass through the...

...the devices of the present invention can be controlled by the release mechanism, the membrane **permeability** , the nature of the excipients, the size of the device and the size **and** number of macropores present in the **skin** of the membrane. In general, release by osmotic pumping releases the active substances **faster** than diffusion, all other factors being the same. Excipients which aid in solubilizing the active substance **enhance** release from the device. Also large and numerous macropores aid in rapid diffusional **release** of the active substances. Another factor which can influence the rate of release is the...

...or more plasticizers in the material used in making the asymmetric membrane can affect the **permeability** of said membrane and hence the **rate** of release of the active substance. In general, hydrophilic plasticizers, such as **glycerine** , will **increase permeability** and release rate **while** hydropholic **plasticizers** , **such** as triethylcitrate will reduce **permeability** and rate of release (Figure 44 - **Example** 52).

The process for preparing a table device surrounded by an asymmetric membrane, wherein the...from a conventional nozzle into a room or chamber. The formation of macropores in the **asymmetric** membrane coated beads is **enhanced** by the nozzle spray drying at a pressure of 68.95 to 689.5 kPa...

...bath for 3 minutes and subsequently into a hexane solvent-exchange bath, also for 3 **minutes** . The tablets were then **allowed** to completely

air-dry for at least 12 hours at room temperature.
The coatings formed...

...a porous layer adjacent to the tablet, extending through almost the entire coating thickness; on **the** outside surface a dense **skin** was formed that was imperforate prior to use. The overall thickness of the membrane coating was approximately 200 (mu)m, and the **thickness** of the dense outer **skin** was less than 1 (mu)m.

EXAMPLE 2

Formation of Asymmetric Membrane Tablet Coating-Wet...

...Trimazosin tablets were dip-coated and quenched in a water bath as described in Example **1** . The tablets were then **allowed** to completely air-dry at room temperature for at least 12 hours.
The coatings formed...

...a porous layer adjacent to the tablet, extending through almost the entire coating thickness; on **the** outside surface a dense **skin** was formed that was imperforate prior to use. The overall thickness of the membrane coatings was approximately 200 (mu)m, and the **thickness** of the dense outer **skin** was less than 1 (mu)m.

EXAMPLE 3

Formation of Asymmetric Membrane Tablet Coating-Dry Process

A coating solution was made of 15 wt% cellulose acetate 398-10 (Eastman Chemical **Products** , Inc.), 1.9 wt% **glycerol** , 2.7 wt% water, 11.7 wt% **butanol** , and 21.7 wt% **ethanol** dissolved in acetone, and the solution stored in a sealed container at room temperature until...described in Examples 1 and 2, the membrane coating consists mostly of a porous sublayer **with** a thin, dense outer **skin** . The overall thickness of the membrane was about 125 (mu)m and **the** thickness of the outer **skin** was about **1** (mu)m. The outer **skin** was imperforate prior to use.

EXAMPLE 4

Osmotic Release from Tablets Coated With Asymmetric Membrane...

...solvent-exchange bath for 3 minutes, followed by immersion in a hexane solvent-exchange bath **for** 3 minutes before being **allowed** to dry to completion at room temperature. The average weight of these coatings was 13...

...made of 15 wt% cellulose acetate 398-10 dissolved in acetone at room temperature. The **tablets** were dip-coated, then **allowed** to air dry before they were dip- **coated** a second time to **increase** the coating thickness. The average weight of these coatings was 25.0 (+-) 2.2 mg...

...coatings were about 65 times higher than those from the same tablets coated with dense **membranes** . This demonstrates higher water **permeability** through asymmetric membrane coatings and subsequently higher release rates compared with dense coatings made of...

...1. A 340-(mu)m diameter hole was mechanically drilled through the coating on some **of** these tablets. The outer **skin** of the coatings was continuous except for the drilled holes.
These tablets were release-rate...

...whereas the osmotic pressure of a saturated solution of trimazosin and the other tablet excipients **was** **about** 304 kPa (about 3 atm). Thus, there was no osmotic **driving** **force** for trimazosin delivery from these tablets into the magnesium sulfate solution. The solubility of trimazosin ...

...as the trimazosin solubility in water, so any difference in release rates from the tablets **placed** **in** magnesium sulfate solution and water

cannot be attributed to different **concentration gradients** across the membrane. Initially the tablets were placed in a stirred solution of 2.4 ...the magnesium sulfate solution by diffusion; the release rate was much higher into water due **to osmotic** pumping of the trimazosin from the tablet. As soon as the osmotic **driving force** was removed (placing the tablets back in a magnesium sulfate solution) the release rate dropped...

...applied in a manner similar to that described in Example 2. The coating solution consisted **of** 15 wt% cellulose acetate 398-10 (Eastman Chemical Products, Inc.) and 33 wt% **ethanol** dissolved in acetone at room temperature. The tablets were dip-coated, air-dried for **five** seconds, then immersed in a water quench bath for four minutes and finally **allowed** to dry to completion at room temperature. All solutions and the entire coating process were...

...the osmotic device do not develop. The same release rates from these doxazosin tablets placed **in** different receptor solutions demonstrate osmotic delivery using asymmetric-membrane coatings.

EXAMPLE 8

Demonstration of Variations of the **Permeability** of Asymmetric Membranes on Coated Tablets

Trimazosin tablets containing 40 wt% trimazosin, 58 wt% Avicel...

...were 150 (mu)m to 250 (mu)m thick. The thickness of the membrane coatings **was** proportional to the quantity of formamide in the coating solution.

Release-rate tests were conducted, comparing relative **permeabilities** of the coatings made with coating solutions with different formamide contents. The coated tablets were placed in water at 37(degree) C. Steady-state release rates **with** respect to the formamide **content** in the coating solution are shown in Figure 6. The release rates **increase** as the formamide content **increases** up to a maximum at a formamide concentration of about 20 wt%. At higher formamide...

...tablet. The point on the graph corresponding to 27 wt% formamide was actually from 280 **mg** trimazosin tablets and was normalized with respect to the surface **area** of the 350 **mg** tablets. The **increasing** release rates indicate that the membrane coatings are becoming more **permeable** to water with **increasing** amounts of formamide and subsequently **higher** release rates are achieved. The membrane coatings with formamide concentrations higher than 20 wt% are evidently less **permeable** than some of the coatings made with coating solutions containing less **formamide** . This phenomenon has been reported in literature describing reverse-osmosis membranes. The ability to vary the membrane **permeability** and subsequently **the** release rate by altering the coating formulation provides added flexibility when designing osmotic delivery systems.

EXAMPLE 9

Enhancement of Osmotic Release Rate From Asymmetric Membrane Coated Tablets

Two types of trimazosin tablets were...ascorbic acid tablets were made with 1 wt% doxazosin, 85 wt% ascorbic acid, 13 wt% **Avicel PH102** (FMC Corp.), and 1 wt% magnesium stearate. The osmotic pressure of a saturated solution of these tablet excipients was about 5.5 MPa (about 54 atm) the osmotic **driving force** in gastric buffers being 4.76 MPa (47 atm), and the doxazosin solubility in a saturated solution of the tablet excipients was about 26 mg/ml.

2) Doxazosin/succinic acid/ **lactose tablets** were made with 1 wt% doxazosin, 49.5% succinic acid, and 49.5% lactose. The...

...solution of these tablet excipients was about 4.76 MPa (about 47 atm).

The osmotic **driving force** in gastric buffer being 4.05 MPa (40 atm), and the doxazosin solubility in a saturated solution of the tablet excipients **was about** 27 mg/ml.

3) Doxazosin/succinic acid tablets were made with 1 wt% doxazosin, 97...

...solution of these tablet excipients was about 2.94 MPa (about 29 atm) the osmotic **driving force** in gastric buffer being 2.23 MPa (22 atm), and the doxazosin solubility in a saturated **solution of** the tablet excipients was about 27 mg/ml.

4) Doxazosin/adipic acid/lactose tablets were...

...solution of these tablet excipients was about 2.53 MPa (about 25 atm) the osmotic **driving force** in gastric buffer being 1.82 MPa (18 atm), and the doxazosin solubility in a saturated solution of the tablet excipients was about 20 mg/ml. **All** of the **tablets** had a total **weight of** 500 mg and contained 5 mg of doxazosin. All of the tablets were coated with...

...2.

Release rates from these tablets into gastric buffer vary from approximately 0.2 mg/ **hr to** 0.6 mg/hr, as shown in Figure 7. The release rates **increased** with an **increase** in the osmotic **driving force as is** characteristic of osmotic delivery systems. The release rate from the doxazosin/adipic acid/lactose tablets...

...the doxazosin solubility was lower than that in the other tablets. Tablets with higher osmotic **driving forces** will build up larger boundary layers within the asymmetric membrane, and the release rates will not be directly proportional to osmotic **driving force** . These data illustrate that the doxazosin release rates can be controlled **by** selecting certain soluble fillers for the tablets.

EXAMPLE 11

Formation of Macropores in Asymmetric Membrane...

...coated as described in Example 2. The coating solutions contained 1 wt%, 5 wt%, 10 **wt** %, and 20 wt% **glycerol** as **a** pore-former in place of formamide. All of the **coating** solutions contained 15 wt% cellulose acetate **398** -10 (Eastman Chemical Products, Inc.) and were dissolved in acetone.

The **coatings** made with these coating solutions were asymmetric **in** structure and similar to the coatings described **in** Example 2, but instead **of** having **a** continuous outer **skin** , **macropores** were formed through the **skin** . More and slightly larger macropores were formed as the **glycerol** concentration in the coating solution was **increased** (Figures 9-12). Coatings made from coating solutions containing 1 wt% **glycerol** do not form macropores through the outer **skin** , but **macropores** were formed on the outer **skin** as the concentration of **glycerol** was **increased** to 5 wt% **glycerol** and greater. These macropores, formed during the coating process, presumably serve as drug-delivery ports.

Trimazosin release rates into water and a 2.4 wt% magnesium **sulfate** solution were determined from tablets coated with solutions containing 1 wt%, 10 wt%, and 20 wt% **glycerol** . Higher release rates into water than those into the magnesium sulfate solution **indicate** osmotic release, as was described in Example 6. The release rates into the two receptor solutions are shown **in** Table I. The coatings made with 1 wt% and 10 wt% **glycerol** appeared to deliver trimazosin osmotically (higher release rates in water than in the magnesium sulfate solution). The release rates from the tablets coated with the solution containing 20 wt% **glycerol**

were the same into the two receptor solutions, which is characteristic of diffusional release. Thus, by controlling the **glycerol** concentration in the coating solution, tablet coatings can be made that facilitate osmotic and/or...

...Asymmetric Membrane

Trimazosin tablets as described in Example 11 were coated with a coating suspension **consisting** of 15 wt% cellulose acetate 398-10 (Eastman Chemical Products, Inc.), 5 wt% sodium acetate...

...in Example 2. The membrane coatings formed on the tablets were asymmetric and the outer **skin** had many macropores through the surface. These macropores were about 1 (mu)m to 5...

...40 wt% trimazosin, 58 wt% Ethocel M50 (Dow Chemical Co.), and 2 wt% magnesium stearate **with** a total weight of 500 mg were coated with asymmetric membranes made of cellulose acetate...

...The three coating solutions contained 1) 15 wt% cellulose acetate 398-10, and 33 wt% **ethanol** dissolved in acetone; 2) 12 wt% Ethocel M50, 16 wt% formamide, and 24 wt% methanol...

...dissolved in acetone.

The trimazosin release rates from all three coated tablets were constant, or **zero** order, for the duration of the tests (7.5 hours), which is typical for osmotic...

...0.22 (+-) 0.11 mg/ml, respectively. Thus, asymmetric-membrane coatings that have different water **permeabilities** and correspondingly different drug release rates.

EXAMPLE 14

Release Rates of Asymmetric Membrane Coated Tablets...

...trimazosin tablets coated by the quench process were larger (350 mg) than those coated by **the** dry process (280 mg). Normalizing the release rates with respect to tablet surface areas, the...

...dry process was 3.9 (+-) 0.4 mg/hr. Thus, the release rate from tablets **coated** by the dry-process membranes was about one third that from tablets coated by the quench process. The dry process coatings are evidently less **permeable** to water than those made by the quench process.

EXAMPLE 15

Asymmetric Membrane Capsules

Capsules...

...solution of 15 wt% cellulose acetate 398-10 (Eastman Chemical Products, Inc.), and 33 wt% **ethanol** dissolved in acetone was used to make the capsules. The solution was kept at room temperature.

Mandrels were made of glass tubes (9 mm and 10 mm outside diameter) **fired** at one end until they were rounded and had a small hole (about 1 mm...

...withdrawn slowly (5 seconds to completely withdraw the mandrels). The coated mandrels were inverted and **allowed** to dry in room-temperature air for 5 seconds and then were immersed in a...

...sliding a tightly fitting collar down each mandrel and sliding the capsules off. The capsules **were** then dried for at least 12 hours in room-temperature air. The dry capsules were...

...capsules and essentially the entire thickness of the capsule wall were porous. The dense outer **skin** was about 1 (mu)m thick, as shown in Figure 13, **and** was continuous and imperforate.

EXAMPLE 16

Osmotic and Diffusional Release from Asymmetric Membrane Capsules

Asymmetric-membrane capsules **were** made in the same manner as described in Example 15. The polymer solution used to **make** these capsules consisted of 17 wt% cellulose acetate 398-10 (Eastman Chemical Products, Inc.), and 30 wt% **ethanol** dissolved in acetone. The capsules were soaked in a 20-wt% **glycerol** solution for at least 12 hours after they were removed from the mandrels. The capsules were then **allowed** to dry at room temperature for at least 12 hours. Soaking the capsules in the **glycerol** solution plasticized the capsules. Once plasticized, the capsules remained flexible and resilient for at least...wt% lactose. The powder was loaded into the body of the capsule, then a thin **band** of adhesive solution was placed around the capsule body such that when the cap of the capsule was placed on the body it would cover the **adhesive** band. Another band of the adhesive solution was then placed around the capsule at the **joint** between the cap and the body. The adhesive solution was 10 wt% cellulose acetate in ethyl acetate. The **adhesive** was **allowed** to dry for at least two hours before the capsules were tested.

The capsules were placed in solutions with different osmotic pressures. The receptor solutions were **dextrose** solutions of various concentrations and gastric buffer (described in Example 7). The pH of the **dextrose** solutions was adjusted to a pH of 4 by adding tartaric acid. The doxazosin solubility in all the **dextrose** solutions was about 10 mg/ml, and the doxazosin solubility **in** **gastric** buffer was about 250 ppm. Release rates from osmotic delivery systems are not dependent on...

...the solution inside the capsule and the receptor solution outside the capsule is the osmotic **driving** **force** . Consequently, the osmotic release rates were inversely proportional to the osmotic pressure of the receptor...

...lower osmotic pressure than a saturated solution of trimazosin and tartaric acid, thus a longer **time** lag from the capsules loaded with trimazosin and calcium lactate would be expected. The rate of water inbibition into the capsules is theoretically proportional to the osmotic **pressure** within the capsule. The even shorter time lag from capsules loaded with a trimazosin in...

...due to a combination of the reduction of the interstitial volume between the powder particles, **better** initial contact with the inside surface of the capsule, and plasticization by the PEG 900, which **may** facilitate quicker wetting of the membrane and a higher water **permeability** . The ability to control the time lag before drug delivery begins may be advantageous for...

...drug-delivery systems that must be released in the intestines or for other specialized drug- **delivery** profiles.

EXAMPLE 18

Macropores in Asymmetric Membrane Capsules

Asymmetric-membrane capsules have been made that have macropores through the outer **skin** of the **capsules** . These macropores function as drug delivery ports through which the drug solution is **pumped** from the capsules. The capsules were made by the same method as described in Example 15. Gycerol was added to the polymer solution and the **ethanol** was removed. The polymer solution consisted of 17 wt% cellulose acetate

398-10 (Eastman Chemical **Products** , Inc.) and 1 wt% to 20 wt% **glycerol** dissolved in acetone. The macropores were more numerous and slightly larger as more **glycerol** was used in the polymer solution and were similar in appearance to the macropores in...

...surface of a capsule wall made with a 17 wt% cellulose acetate and 3 wt% **glycerol** solution in acetone is shown in Figure 15. The macropores through the surface and the...

...the exterior of the capsule, and a steady stream flows to the bottom of the **container** . In capsules that do not have macropores through the surface, the dextran blue is pumped...

...flows to the bottom of the container. Thus, macropores can be formed through the outer **skin** of asymmetric membrane capsules and appear to function as drug-delivery ports for osmotic drug...described in Example 15. The Ethocel polymer solution consisted of 12 wt% Ethocel M50, 16 **wt** % formamide, and 24 wt% methanol dissolved in methyl acetate, and the cellulose acetate butyrate polymer...

...approximately 300 (mu)m and 450 (mu)m, respectively. The thickness of the dense outer **skin** for both these capsules was about 1 (mu)m. All of the capsules were loaded...

...trimazosin in PEG 900 slurry at about 37(degree) C. (PEG 900 is a solid **at** room temperature.) The capsules were sealed with an epoxy adhesive as described in Example 16...

...of cellulose acetate, Ethocel, and cellulose acetate butyrate, respectively. These data illustrate the different water **permeabilities** in the polymers investigated and how these properties can be utilized to formulate osmotic capsules...

...to non-pareil beads (20- to 25-mesh, or about 1 mm in diameter) with **a** spray-coating process. The beads were mixed with the **polymer** coating solution, then sprayed through an external-mixing air-atomizing nozzle (Model 100150) available from...

...a 38-wt% nonsolvent mixture dissolved in acetone. The nonsolvent mixture consisted of 57 wt% **ethanol** , 31 wt% butanol, 7 wt% water, and 5 wt% **glycerol** .

The beads and polymer solution were mixed just upstream from the spray nozzle, and the...

...were similar in appearance to the dry-process asymmetric-membrane tablet coatings described in Example **3** . The asymmetric-membrane coatings on beads were much thinner than the dry-process coatings on...

...tablets and beads were porous through essentially the entire thickness and had a dense outer **skin** that was approximately 1 (mu)m thick.

EXAMPLE 21

Multiple Coatings of Asymmetric Membrane on...

...The coating process was repeated three times, and after each coating a quantity of beads **were** set aside; thus, beads were obtained with single, double, and triple coatings. The overall coating thickness varied from 5 (mu)m to **15** (mu)m for the single-coated beads, from 10 (mu)m to 25 (mu)m for the **double** -coated beads, and 20 (mu)m to 30 (mu)m for the triple-coated beads, as determined by SEM observation. The outer **skin** of the coatings was dissolved by the subsequent coatings, leaving a

homogeneous porous layer through the entire coating except for an outer **skin** that was approximately 1 (mu)m thick, as shown by the example in Figure 17. The outside **skin** was the same for single, double and triple coatings.

Release rates were determined from **these** beads (65 mg) into a lactose solution with an osmotic pressure of 709 kPa (7...

...from beads that were coated more times, as shown in Figure 18. This was probably **due** to the **increase** in overall thickness of the asymmetric coating as additional coatings were applied.

EXAMPLE **22**

Osmotic Release From Asymmetric Membrane Coated Beads

Triple-coated doxazosin beads, as described in Example...

...of 0 kPa), a lactose solution with an osmotic pressure of 709 kPa (7 atm), **and** **a** **dextrose** solution with an osmotic pressure of 2.03 MPa (20 atm). Tartaric acid was added to the lactose and **dextrose** solutions to adjust the pH to 4 so that the doxazosin solubility, 10 mg/ml...

...rates from the beads into the different receptor solutions will not be due to different **concentration** **gradients** across the membrane coatings, and the diffusional contribution to the drug **release** **from** the beads is the same in all cases. The doxazosin-release rates into these three...at the point when 0.6 mg of doxazosin had been released, decreasing the osmotic **driving** **force** and the **doxazosin** -release rate. The dependence of the release rates on the osmotic pressure, or more precisely...

...solution at room temperature (same polymer coating solution as that described in Example 20). The **beads** and coating solution were placed in a pressure vessel, and 276 kPa (40 psi) was applied to the vessel. The beads and polymer **solution** were sprayed out an airless nozzle (a hose connector with a 3-mm diameter orifice...

...nozzle caused bubbles to form in the coating solution, thus forming macropores through the outer **skin** as the coating precipitates (Figure 20). The same coating solution (and conditions) but applied without a pressure drop forms a continuous, dense **outer** **skin** , as described in Example 3.

EXAMPLE 24

Formation of Asymmetric Membrane Coated Beads-Wet Process...

...to form asymmetric osmotic beads. The polymer coating solution was made of 15 wt% cellulose **acetate** 398-10 (Eastman Chemical Products, Inc.), and 33 wt% **ethanol** dissolved in acetone and was used at room temperature. A mixture of beads and coating...

...beads were kept in the water quench bath for about a minute then removed and **allowed** to air-dry at room temperature for at least 12 hours. These asymmetric beads had...

...to 3 mm and a skinned outer surface. Inside the particles was a porous cellulose **acetate** **network** . Any trimazosin beads present were dispersed in the porous cellulose acetate network. Osmotic release of...

...Figure 21. The solubility of trimazosin is the same in both solutions; thus, the 75% **decrease** in release rate into the magnesium sulfate solution was due to reduction of the osmotic **driving** **force** across the membrane coating, demonstrating osmotic release.

EXAMPLE 25

Formation of Macropores in Asymmetric Membranes...

...were dip-coated with a solution consisting of 15 wt% CA 398-10, 30 wt% **ethanol** , and 55 wt% acetone. The coated tablets were air-dried for 5 seconds and then immersed in a 60(**degree**) C. water quench bath for 5 minutes. After the coated tablets were removed from the...

...temperature and humidity. These membrane coatings were asymmetric and had macropores in the outer surface **of** the coating. Small bubbles could be seen forming on the surface of the membrane coating as it precipitated **in** the quench bath. Several of these bubbles ruptured the **skin** of the membrane coating forming macropores that could serve as drug-delivery ports.

EXAMPLE 26

Formation of Macropores in Asymmetric Membranes

Doxazosin tablets as described in Example **25** were dip-coated with a solution consisting of 15 wt% CA 398-10, 30 wt% **ethanol** , and 55 wt% acetone. The coated tablets were air-dried for 5 seconds and then immersed in an **ethanol** quench bath at ambient temperature for 5 minutes. After the tablets were removed from the...

...air-dried for at least 12 hours at ambient conditions. The membrane coatings were asymmetric **and** the outer **skin** had many macropores through the surface. These macropores were about 1 (mu)m in diameter...

...ethylcellulose (Ethocel std-45, Dow Chemical, Midland, Michigan), 25 wt% acetic acid, and 5 wt% **glycerol** dissolved in acetone.

Capsules were made using two sizes of mandrels--one size for the...

...seconds and then immersed in a 45(degree)C quench bath that contained 5 wt% **glycerol** in water. The coated mandrels were removed from the quench bath after 30 minutes, and...

...capsule caps and bodies were removed from the mandrels by sliding a tight collar down **each** mandrel to force the caps and bodies off the mandrels. The capsule caps and bodies...

...the capsule wall, including the inside surface of the capsule, was porous. The dense outer **skin** was less than 1 (mu)m thick **and** , as shown in **Figure** 22, was continuous and imperforate.

These capsules were loaded with 200 mg of a powder...that contained 15 wt% cellulose acetate (CA 398-10, Eastman Chemicals, Kingsport, Tennessee), 8 wt% **glycerol** , and 25 wt% **ethanol** dissolved in acetone. The volatile solvents were evaporated, leaving a cellulose acetate seal that prevented...

...atm) and pH of 7.5) at 37(degree)C. About 70% of the glipizide **was** released at a **constant** rate--a release pattern that is typical of osmotic-delivery systems. The steady-state release...

...of 15 wt% cellulose acetate butyrate (CAB 381-20, Eastman Chemicals, Kingsport, Tennessee), 30 wt% **ethanol** , **and** 5 wt% **glycerol** dissolved in acetone.

Capsules were made using two sizes of mandrels--one size for the capsule cap and one size for the capsule body. The mandrels were immersed in room- **temperature** coating solution and were withdrawn slowly, taking 9 seconds to completely withdraw the mandrels. The...

...7 seconds and then immersed in a room-temperature quench bath that contained 5 wt% **glycerol** in water. The coated mandrels were removed from the quench bath after 30 minutes, and the capsule caps and bodies

removed from the mandrels by sliding a tight collar **down** each mandrel to force the caps and bodies off the mandrels. The capsule caps and...

...the capsule wall, including the inside surface of the capsules, was porous. The dense outer **skin** was less than 1 (mu)m thick **and** , as shown in **Figure** 23, was continuous and imperforate.
These capsules were loaded with 200 mg of a powder...

...that contained 15 wt% cellulose acetate (CA 398-10, Eastman Chemicals, Kingsport, Tennessee), 8 wt% **glycerol** , and 25 wt% **ethanol** dissolved in acetone. The volatile solvents were evaporated, leaving a cellulose acetate seal that prevented...

...C. About 70% of the glipizide was released at a constant rate--a release pattern **typical** of osmotic-delivery **systems** . The steady-state release rate of glipizide (during the period of constant release) was 1...

...Chemical, Midland, Michigan), 2 wt% cellulose acetate (CA 398-10, Eastman Chemicals, Kingsport, Tennessee), 30 **wt** % **ethanol** , and 10 wt% **glycerol** dissolved in acetone.
Capsules were made using two sizes of mandrels--one size for the capsule cap and one size for the capsule body. The mandrels were immersed **in** room- **temperature** coating solution and were withdrawn slowly, taking 9 seconds to completely withdraw the mandrels. The...

...7 seconds and then immersed in a room-temperature quench bath that contained 5 wt% **glycerol** in water. The coated mandrels were removed from the quench bath after 30 minutes, and...

...can function as drug-delivery ports. Thus, blending two incompatible polymers can be used to **form** asymmetric-membrane capsules **or** coatings that contain macropores in the surface.
These capsules were loaded with 200 mg of...

...that contained 15 wt% cellulose acetate (CA 398-10, Eastman Chemicals, Kingsport, Tennessee), 8 wt% **glycerol** , and 25 wt% **ethanol** dissolved in acetone. The volatile solvents were evaporated, leaving a cellulose acetate seal that prevented...

...About 70% of the glipizide was released at a constant rate--a release pattern that **is** typical of osmotic- **delivery** systems. The steady-state release rate of glipizide (during the period of constant release) was... 20, Eastman Chemicals, Kingsport, Tennessee), 2 wt% ethylcellulose (Ethocel std-100, Dow Chemical, Midland, Michigan), **30** wt% **ethanol** , and 5 wt% 1glycerol dissolved in acetone.
Capsules were made using two sizes of mandrels--one size for the capsule cap and one size for the capsule body. The mandrels were immersed **in** room- **temperature** coating solution and were then withdrawn slowly, taking 7 seconds to completely withdraw the mandrels...

...7 seconds and then immersed in a room-temperature quench bath that contained 5 wt% **glycerol** in water. The coated mandrels were removed from the quench bath after 30 minutes, and the capsule bodies and caps were removed from the mandrels by sliding a tight **collar** down each mandrel to force the caps and bodies off the mandrels. The capsule bodies and caps were dried in room-temperature air for at **least** 12 hours and then trimmed to the desired lengths.
Capsule bodies and caps formed by...
...the capsule wall, including the inside surface of the capsule, was porous. The dense outer **skin** was less than 1 (mu)m thick and had many

dimples, as shown in Figure 25. The dimples **appear** to contain macropores **in** the outer **skin** , which could serve as drug-delivery ports.

The capsules were loaded with 200 mg of...

...solution containing 15 wt% cellulose acetate (CA 398-10, Eastman Chemicals, Kingsport, Tennessee), 8 wt% **glycerol** , and 25 wt% **ethanol** dissolved in acetone. The volatile solvents were evaporated, leaving a cellulose acetate seal that prevented...

...70% of the glipizide was release at a constant rate--a release pattern that is **typical** of osmotic-delivery **systems** . The steady-state release rate of glipizide (during the period of constant release) was 1...

...20, Eastman Chemicals, Kingsport, Tennessee), 3 wt% cellulose acetate (CA 398-10, Eastman Chemicals, Kingsport, **Tennessee**), 30 wt% **ethanol** , and 5 wt% **glycerol** dissolved in acetone.

Capsules were made using two sizes of mandrels--one size for the...

...seconds and then immersed in a 42(degree)C quench bath that contained 5 wt% **glycerol** in water. The coated mandrels were removed from the quench bath after 30 minutes, and the capsule caps and bodies removed from the mandrels by sliding **a** tight collar down each mandrel to force the caps and bodies off the mandrels. The...

...the capsule wall, including the inside surface of the capsule, was porous. The dense outer **skin** was less than **1** (mu)m **thick** and, as shown in Figure 26, was continuous and imperforate.

The capsules were loaded with...

...solution containing 15 wt% cellulose acetate (CA 398-10, Eastman Chemicals, Kingsport, Tennessee), 8 wt% **glycerol** , and 25% **ethanol** dissolved in acetate. The volatile solvents were evaporated, leaving a cellulose acetate seal that prevented...

...osmotic pressure of 709 kPa (7 atm) and pH of 7.5) at 37(degree) **C** . About 70% of the glipizide was released at a constant rate--a release pattern that...

...asymmetric-membrane walls were made from a solution of 34 wt% cellulose acetate propionate (CAP **482** -0.5, Eastman Chemicals, Kingsport, Tennessee), and 10 wt% **glycerol** dissolved in acetone.

Capsules were made using two sizes of mandrels--one size for the...

...3 seconds and then immersed in a room-temperature quench bath that contained 15 wt% **glycerol** in water. The coated mandrels were removed from the quench bath after 30 minutes, and the capsule caps and bodies were removed from the mandrels by sliding a **tight** collar down ...had walls about 450 (mu)m thick that were asymmetric in structure. Essentially the entire **thickness** of the capsule walls, including the inside surface of the capsules, was porous, as shown in Figure 27. The dense outer **skin** was less then 1 (mu)m thick and contained many macropores, which would function as...

...made from a solution of 36.5 wt% nitrocellulose (nitrocellulose RS 18-25, Hercules, Inc., **Wilmington** , Delaware), 13.5 wt% isopropanol, and 15 wt% **glycerol** dissolved in acetone.

Capsules were made using two sizes of mandrels--one size for the...

...7 seconds and then immersed in a room-temperature quench bath that

contained 15 wt% **glycerol** in water. The coated mandrels were removed from the quench bath after 30 minutes, and the capsule caps and bodies were removed from the mandrels by sliding a **tight** collar down each mandrel to force the caps and bodies off the mandrels. The capsule...

...and then trimmed to the desired lengths.

Capsules formed by the process described above had **walls** about 400 (mu)m **thick** that were asymmetric in structure. Essentially the entire thickness of the capsule walls, including the inside surface of the capsules, was porous, as shown in Figure 28. The dense outer **skin** was less than 1 (mu)m thick.

EXAMPLE 34

Formation of Asymmetric-Membrane Capsules Made...

...of 23.6 wt% cellulose acetate phthalate (CAPh, Eastman Chemicals, Kingsport, Tennessee), 25.5 wt% **ethanol** , and 7.3 wt% **glycerol** dissolved in acetone.

Capsules were made using two sizes of mandrels--one size for the capsule cap and one size for the capsule body. The mandrels were immersed **in** room- **temperature** coating solution and were withdrawn slowly, taking 7 seconds to completely withdraw the mandrels. The...

...minutes, and the capsule caps and bodies were removed from the mandrels by sliding a **tight** collar down each mandrel to force the caps and bodies off the mandrels. The capsule...

...desired lengths.

Capsules formed by the process described above had walls about 200 (mu)m **thick** that were asymmetric in structure. Essentially the entire thickness of the capsule walls, including the inside surface of the capsules, was porous, as shown in Figure 29. The dense outer **skin** was less than 1 (mu)m thick and was continuous and imperforate.

EXAMPLE 35

Formation...

...solution of 25 wt% cellulose acetate trimellitate (CAT, Eastman Chemicals, Kingsport, Tennessee), and 25 wt% **ethanol** dissolved in acetone.

Capsules were made using two sizes of mandrels--one size for the capsule cap and one size for the capsule body. The mandrels were immersed **in** room- **temperature** coating solution and were withdrawn slowly, taking 10 seconds to completely withdraw the mandrels. The...

...minutes, and the capsule caps and bodies were removed from the mandrels by sliding a **tight** collar down each mandrel to force the caps and bodies off the mandrels. The capsule...

...the desired lengths.

Capsules formed by the process described above had walls about 400 (mu) **m** thick that were asymmetric in structure. Essentially the entire thickness of the capsule walls, including...

...inside surface of the capsules, was porous, as shown in Figure 30. The dense outer **skin** was less than 1 (mu)m thick and was continuous and imperforate.

EXAMPLE 36

Formation...

...solution of 15 wt% polyvinyl alcohol (Elvanol 71-30, Dupont, Wilmington, Delaware), and 20 wt% **ethanol** dissolved in water.

Capsules were made using two sizes of mandrels--one size for the...

...minutes, and the capsule caps and bodies were removed from the mandrels by sliding a **tight** collar down each mandrel to force the caps and bodies off the mandrels. The capsule...the capsule walls, including the inside surface of the capsules, was porous, as shown in **Figure** 31. The dense **outer skin** was approximately 50 (mu)m thick and continuous and imperforate.
These capsules were loaded with...

...that contained 15 wt% cellulose acetate (CA 398-10, Eastman Chemicals, Kingsport, Tennessee), 8 wt% **glycerol** , and 25 wt% **ethanol** dissolved in acetone. The volatile solvents were evaporated, leaving a cellulose acetate seal that prevented...

...solution of simulated intestinal buffer (osmotic pressure of 709 kPa (7 atm) and pH of 7 .5) at 37(degree)C. About 90% of the glipizide was released at a constant...

...15 wt% ethylenevinyl alcohol (EVAL F-101, EVAL Co. of America, Omaha, Nebraska), 55 wt% **ethanol** , and 30 wt% water.
Capsules were made using two sizes of mandrels--one size for...

...after 30 minutes, and the capsule caps and bodies were removed from the mandrels by **sliding** a tight collar down each mandrel to force the caps and bodies off the mandrels...

...of the capsule walls, including the inside surface of the capsules, was porous, as shown **in** Figure 32. The **dense** outer **skin** was less than 1 (mu)m thick and was continuous and imperforate.
These capsules were...

...that contained 15 wt% cellulose acetate (CA 298-10, Eastman Chemicals, Kingsport, Tennessee), 8 wt% **glycerol** , and 25 wt% **ethanol** dissolved in acetone. The volatile solvents were evaporated, leaving a cellulose acetate seal that prevented...

...bath after 30 minutes, and the capsule caps and bodies were removed from the mandrels **by** sliding a tight collar down each mandrel to force the caps and bodies of the...

...thickness of the capsule walls, including the inside surface of the capsules, was porous, as **shown** in Figure 33. **The**0 dense outer **skin** was less than 1 (mu)m thick and was continuous and imperforate.
These capsules were...

...solution containing 15 wt% cellulose actate (CA 398-10, Eastman Chemicals, Kingsport, Tennessee), 8 wt% **glycerol** , and 25 wt% **ethanol** dissolved in acetone. The volatile solvents were evaporated, leaving a cellulose acetate seal that prevented...from the quench bath after 30 minutes, and the capsule caps and bodies were removed **from** the mandrels by sliding a tight collar down each mandrel to force the caps and...

...the entire thickness of the capsule walls, including the inner surface of the capsules, was **porous** , as shown in **Figure** 34. The outer **skin** was covered with many pores less than 1 (mu)m in diameter.
These capsules were...

...that contained 15 wt% cellulose acetate (CA 398-10, Eastman Chemicals, Kingsport, Tennessee), 8 wt% **glycerol** , and 25 wt% **ethanol** dissolved in acetone. The volatile solvents were evaporated, leaving a cellulose

acetate seal that prevented...

...removed from the quench bath after 30 minutes, and the capsule caps and bodies were **removed** from the mandrels by sliding a tight collar down each mandrel to force the caps...

...Essentially the entire thickness of the capsule walls, including the inside surface of the capsule, **was** porous, as shown **in** Figure 35. The dense outer **skin** was less than 1 (mu)m thick and was continuous and imperforate.

These capsules were...

...that contained 15 wt% cellulose acetate (CA 398-10, Eastman Chemicals, Kingsport, Tennessee), 8 wt% **glycerol** , and 25 wt% **ethanol** dissolved in acetone. The volatile solvents were evaporated, leaving a cellulose acetate seal that prevented...

...mandrels were removed from the quench bath after 30 minutes, and the capsule caps and **bodies** were removed from the mandrels by sliding a tight collar down each mandrel to force...

...air for at least 12 hours and then trimmed to the desired lengths.

Capsules formed **by** the process described above had walls about 200 (mu)m thick that were asymmetric in...

...inside surface of the capsules, was porous, as shown in Figure 36. The dense outer **skin** was about 5 (mu)m thick and was continuous and imperforate.

EXAMPLE 42

Formation ofDupont, Wilmington, Delaware), 19 wt% water, and 56 wt% **ethanol** .

Capsules were made using two sizes of mandrels--one size for the capsule cap and...

...mandrels were removed from the quench bath after 30 minutes, and the capsule caps and **bodies** were removed from the mandrels by sliding a tight collar down each mandrel to force...

...asymmetric in structure. Most of the thickness of the capsule walls, including the inside surface **of** the capsules, was **porous** , as shown in Figure 37. The dense outer **skin** was about 11 (mu)m thick and was continuous and imperforate.

These capsules were loaded...

...that contained 15 wt% cellulose acetate (CA 398-10, Eastman Chemicals, Kingsport, Tennessee), 8 wt% **glycerol** , and 25 wt% **ethanol** dissolved in acetone. The volatile solvents were evaporated, leaving a cellulose acetate seal that prevented...

...during release-rate tests.

For release-rate tests, loaded capsules were placed in a stirred **solution** of simulated intestinal **buffer** (osmotic pressure of 709 kPa (7 atm) and pH of 7.5) at 37(degree...

...asymmetric-membrane walls were made from a coating solution of 10 wt% ethylcellulose (Ethocel std- **100** , Dow Chemicals, Midland, Michigan), 2 wt% cellulose acetate phthalate (CAPh, Eastman Chemicals, Kingsport, Tennessee), 30 wt% **ethanol** , and 10 wt% **glycerol** dissolved in acetone.

Capsules were made using two sizes of mandrels--one size for the...

...7 seconds and then immersed in a room-temperature quench bath that

contained 5 wt% **glycerol** in water. The coated mandrels were removed from the quench bath after 30 minutes, and the capsule **caps** and bodies were removed from the mandrels by sliding a tight collar down each mandrel...

...m thick that were asymmetric in structure. Essentially the entire thickness of the capsule walls, **including** the inner surface **of** the capsules, was porous, as shown in Figure 38. The dense outer **skin** had macropores on the surface, which could serve as drug-delivery ports. The macropores were...

...asymmetric-membrane walls were made from a coating solution of 10 wt% ethylcellulose (Ethocel std- **100** , Dow Chemicals, Midland, Michigan), 2 wt% cellulose acetate trimellitate (CAT, Eastman Chemicals, Kingsport, Tennessee), 30 wt% **ethanol** , and 10 wt% **glycerol** dissolved in acetone.

Capsules were made using two sizes of mandrels--one size for the...

...7 seconds and then immersed in a room-temperature quench bath that contained 5 wt% **glycerol** in water. The coated mandrels were removed from the quench bath after 30 minutes, and the capsule **caps** and bodies were removed from the mandrels by sliding a tight collar down each mandrel...

...inside surface of the capsules, was porous, as shown in Figure 39. The dense outer **skin** appeared to have macropores through the surface, which could serve as drug-delivery ports. The...

...and 75 wt% acetone. The polymer solution was kept at 40(degree)C and the **drying** chamber was kept at 70(degree)C. The **beads** were mixed with the polymer solution just upstream from the spray nozzle and the mixture...m thick. The entire thickness of the coating was porous except for a dense outer **skin** , as shown in Figure 40. The dense outer **skin** was less than 1 (mu)m thick and was continuous and imperforate over the entire...

...Delaware), 14 wt% methyl ethyl ketone, 3 wt% water and 52 wt% acetone. The polymer **solution** was kept at 45(degree)C and the drying chamber was kept at 80(degree)C. **The** beads were mixed with the polymer solution just upstream from the spray nozzle and the...

...asymmetric-membrane coating that was approximately 20 (mu)m thick. Except for a dense outer **skin** , the entire thickness of the coating was porous, as shown in Figure 41. The dense outer **skin** was less than 1 (mu)m thick and was continuous and imperforate over the entire...

...were made with several different polymers, including polyvinyl alcohol (PVA), polyvinylidene fluoride (PVDF), and blends **of** **cellulose** acetate butyrate (CAB) and cellulose acetate; CAB and ethylcellulose (Ethocel); and Ethocel and CA. The...

...open end of the capsule above the surface of the buffer. Due to the osmotic **driving** **force** , water was imbibed into the capsule bodies. The water imbibed into the capsule bodies was measured by weight gain until the solution inside the capsule body filled the capsule body **and** overflowed into the intestinal buffer.

Release-rate tests, such as **those** described in Examples 29, 30, 31, 36 and 39, were conducted. The capsules were loaded **with** the same powder mixture as that used to load the capsule bodies for the water...

...water flux is shown in Figure 42 for each type of capsule. The release

rates **increase** as the water fluxes through the asymmetric-membrane capsule walls **increase** , as predicted by osmotic theory. Thus, by using the asymmetric-membrane capsules with the proper **permeability** to water, the desired release rate can be achieved without changing the composition of the material loaded in the capsules.

EXAMPLE 48

Using standard techniques well known in the pharmaceutical **industry** , 3/8 inch modified ball shape tablets were prepared to contain: (see image in original...

...model HCT 30) using a coating solution of the following composition:

acetone	50.0 wt%
ethanol	22.8 wt%
n-butanol	12.4 wt%
water	2.8 wt%
glycerol	2.0 wt%
cellulose acetate 398-10	10.0 wt%

The coating process was stopped...

...a largely porous layer which accounted for most of the coating thickness, surmounted by a **skin** which was perforated by numerous pores, but which was much less porous in appearance than...

...and coated with a solution having the composition:

cellulose acetate 398-10	5%
acetone	55%
ethanol 95% USP	40%

After the beads had received coating equivalent to 4.7 wt% cellulose...in the quench bath, the coated mandrels were withdrawn and dried at room temperature for **about** 30 minutes. After the drying step, the capsule shells were stripped off the pins using...

...and the other half had pins corresponding to capsule caps. The capsule dosage form was **assembled** by filling the capsule body with a powder composition consisting of an active agent and...

...electron microscope (SEM). The membrane was asymmetric with a relatively thin (6 (mu)m) dense **skin** formed on the surface of the capsule that was away from the mold pin and...

...Capsules were made from cellulose acetate as in Example 51 but with different ratios of **glycerol** /triethylcitrate. They were filled with a mixture of glipizide, meglumine, and sodium bicarbonate, and sealed...

...CLAIMS or more asymmetric membranes.

2. A device according to claim 1, wherein the membrane is **permeable** and is either imperforate or perforate.
3. A device according to claim 1, wherein the...

...is dazmergrel.

16. A device according to claim 9, wherein the substance is a blood-**glucose** lowering agent.
17. A device according to claim 16, wherein the substance is glipizide.
18...

...present in the amount of 15 by weight and the pore-forming substances are formamide, **acetic** acid, **glycerol** , an alkanol of one to four carbon atoms, sodium acetate, aqueous hydrogen peroxide or polyvinylpyrrolidone.

24. The process of claim 23 wherein the pore-forming **substance** is

ethanol present in the amount of 30% by weight.

25. The process of claim 23 wherein the pore-forming **substance** is **glycerol** present in the amount of 10% by weight.
26. The process of claim 21 comprising...

...398-10 present in the amount of 15% by weight and the pore-forming substances **are** formamide, acetic acid, **glycerol** , an alkanol of one to four carbon atoms, sodium acetate, aqueous hydrogen peroxide or polyvinylpyrrolidone.

28. The process of claim 27 wherein the **pore** -forming substance is **ethanol** present in the amount of 30% by weight.
29. The process of claim 20 wherein...

...is cellulose acetate 398-10 present in the amount of 15% by weight and the **pore** -forming substances are **comprised** of **glycerol** , water, butanol and **ethanol** present in the amount of 1.9, 2.7, 11.7 and 21.7%, respectively...ester is cellulose acetate 398-10 present in the amount of 16% by weight and **the** pore-forming substance is formamide, acetic acid, **glycerol** , an alkanol of one to four carbon atoms, sodium acetate, aqueous hydrogen peroxide or polyvinylpyrrolidone.

36. The process of **claim** 35 **wherein** the pore-forming substances are **ethanol** and **glycerol** present in the amount of 28 and 8%, respectively, by weight.
37. The process of **claim** 35 wherein the pore-forming substance is **glycerol** present in the amount of 10% by weight.
38. A process for preparing beads for...

...the polymer flakes by sieving or by using cyclones.

41. The process of claim 40 **wherein** the pore-forming **substance** , which comprises 38% by weight of the total solution and consists of **ethanol** , butanol, water and **glycerol** present in the amount of 57, 31, 7 and 5%, respectively, by weight and the...

...c) removing the beads after the membrane has solidified and drying.

45. The process of **claim** 44 wherein the cellulose ester is cellulose acetate 398-10 present in the amount of 15% by weight and the pore-forming substance is **ethanol** present in the amount of 33% by weight.
46. A capsule device for the controlled...

...device comprising a core of said substances, with or without excipients, enclosed in a capsule **the** top or bottom of which is comprised of one or more asymmetric membranes.

47. A device of claim 46, wherein the membrane is **permeable** and perforate or imperforate.
48. A device of claim 47, wherein the release is by...

...of the desired capsule, with a solution comprised of from 10 to 20% of a **cellulose** ester or ethyl cellulose by weight and, optionally, from 0 to 40% of one or...

...the amount of 16% by weight and the pore-forming substance is formamide, acetic acid, **glycerol** , an alkanol of one to four carbon atoms, sodium acetate, aqueous hydrogen peroxide or polyvinylpyrrolidone.

53. The process of claim 52, wherein the pore-forming substances are **ethanol** and **glycerol** present in the amount of 28 and 8%, respectively, by weight.
54. The process of claim 52, wherein the pore-forming substance is **glycerol** present in the amount of 10% by weight.
55. A process for preparing a bead...

...controlled release of one or more active substances into an environment of use, said device **comprised** of a core of said active substances, with or without one or more excipients, surrounded by more than one asymmetric membrane wherein said membranes are formed by **a** phase **inversion** process.

56. The process of claim 55, wherein the process is a dry process.

57. The process of claim 56, comprising the spray **coating** of said device suspended in the temperature controlled air flow of a fluidized bed coating...

...have been applied.

58. The process of claim 57, wherein the pore-forming substance is **ethanol** and the cellulose ester is cellulose acetate 398-10.

59. A process for preparing a...a dry process.

61. The process of claim 60, comprising spray coating said core in **a** perforated pan coating machine with a solution comprised of from 10 to 15% of a...

...present in the amount of 16% by weight and the pore-forming substance is formamide, **acetic** acid, **glycerol** , an **alkanol** of one to four carbon atoms, sodium acetate, aqueous hydrogen peroxide or polyvinylpyrrolidone.

36. The process of claim 35 wherein the pore-forming substances are **ethanol** and **glycerol** present in the amount of 28 and 8%, respectively, by weight.

37. The process of claim 35 wherein the pore-forming substance is **glycerol** present in the amount of 10% by weight.

38. A process for preparing beads for...

...pore-forming substance, which comprises 38% by weight of the total solution and consists of **ethanol** , butanol, water and **glycerol** present in the amount of 57, 31, 7 and 5%, respectively, by weight and the...

...10 present in the amount of 15% by weight and the pore-forming substance is **ethanol** present in the amount of 33% by weight.

46. A method for releasing one or...

...tablet, capsule or bead.

48. A method of claim 47 wherein the asymmetric membrane is **permeable** and imperforate or perforate.

49. A method of claim 48 wherein the releasing is substantially...

...one or more asymmetric membranes.

54. A device of claim 53 wherein the membrane is **permeable** and perforate or imperforate.

55. A device of claim 54 wherein the release is by...

...the amount of 16% by weight and the pore-forming substance is formamide, acetic acid, **glycerol** , an alkanol of one to ...peroxide or polyvinylpyrrolidone.

60. The process of claim 59 wherein the pore-forming substances are **ethanol** and **glycerol** present in the amount of 28 and 8%, respectively, by weight.

61. The process of claim 59 wherein the pore-forming substance is **glycerol** present in the amount of 10% by weight.

62. A process for preparing a bead...

...have been applied.

65. The process of claim 64 wherein the pore-forming substance is **ethanol** and the cellulose ester is cellulose acetate 398-10.

66. A process for preparing a...

...in the amount of 10% by weight and the pore-forming substances are comprised of **glycerol** , water, butanol and **ethanol** present in the amount of 2, 2.8, 12.4 and 22, respectively, by weight...

...in the amount of 10% by weight and the pore-forming substances are comprised of **glycerol** , water, butanol and **ethanol** present in the amount of 2, 2.8, 12.4 and 22, respectively, by weight. ...
...CLAIMS ist, das in einer Menge von 15 Gew.-% vorliegt, und die porenbildenden Substanzen Formamid, Essigsaure. **Glycerin** , ein Alkanol mit 1 bis 4 Kohlenstoffatomen, Natriumacetat, wasriges Wasserstoffperoxid oder Polyvinylpyrrolidon sind.

24. Verfahren nach Anspruch 23, worin die porenbildende Substanz **Ethanol** ist, das in einer Menge von 30 Gew.-% vorliegt.
25. Verfahren nach Anspruch 23, worin die porenbildende Substanz **Glycerin** ist, das in einer Menge von 10 Gew.-% vorliegt.
26. Verfahren nach Anspruch 21, das...

...ist, das in einer Menge von 15 Gew.-% vorliegt, und die porenbildenden Substanzen Formamid, Essigsaure, **Glycerin** , ein Alkanol mit 1 bis 4 Kohlenstoffatomen, Natriumacetat, wasriges Wasserstoffperoxid oder Polyvinylpyrrolidon sind.

28. Verfahren nach Anspruch 27, worin die porenbildende Substanz **Ethanol** ist, das in einer Menge von 30 Gew.-% vorliegt.
29. Verfahren nach Anspruch 20, worin...

...398-10 ist, das in einer Menge von 15 Gew.-% vorliegt, und die porenbildenden Substanzen **Glycerin** , Wasser, Butanol und **Ethanol** sind, die in einer Menge von 1,9, 2,7, 11,7 bzw. 21,7...
...ist, das in einer Menge von 16 Gew.-% vorliegt, und die porenbildende Substanz Formamid, Essigsaure, **Glycerin** , ein Alkanol mit 1 bis 4 Kohlenstoffatomen, Natriumacetat, wasriges Wasserstoffperoxid oder Polyvinylpyrrolidon ist.

36. Verfahren nach Anspruch 35, worin die porenbildenden Substanzen **Ethanol** und **Glycerin** sind, die in einer Menge von 28 bzw. 8 Gew.-% vorliegen.
37. Verfahren nach Anspruch 35, worin die porenbildende Substanz **Glycerin** ist, das in einer Menge von 10 Gew.-% vorliegt.
38. Verfahren zur Herstellung von Perlen...

...nach Anspruch 40, worin die porenbildende Substanz, die 38 Gew.-% der gesamten Losung ausmacht, aus **Ethanol** , Butanol, Wasser und **Glycerin** besteht, die in einer Menge von 57, 31, 7 bzw. 5 Gew.-% vorliegen, und der...

...398-10 ist, das in einer Menge von 15 Gew.-% vorliegt, und die porenbildende Substanz **Ethanol** ist, das in einer Menge von 33 Gew.-% vorliegt.

46. Kapselvorrichtung zur kontrollierten Freigabe einer...

...ist, das in einer Menge von 16 Gew.-% vorliegt, und die porenbildende Substanz Formamid, Essigsaure, **Glycerin** , ein Alkanol mit 1 bis 4 Kohlenstoffatomen, Natriumacetat, wasriges Wasserstoffperoxid oder Polyvinylpyrrolidon ist.

53. Verfahren nach Anspruch 52, worin die porenbildenden Substanzen **Ethanol** und **Glycerin** sind, die in einer Menge von 28 bzw. 8 Gew.-% vorliegen.
54. Verfahren nach Anspruch 52, worin die porenbildende Substanz **Glycerin** ist, das in einer Menge von 10 Gew.-% vorliegt.

55. Verfahren zur Herstellung einer Perlen...

...Anzahl asymmetrischer Membranen aufgebracht worden ist.
58. Verfahren nach Anspruch 57, worin die porenbildende Substanz **Ethanol** und der Celluloseester Celluloseacetat 398-10 sind.
59. Verfahren zur Herstellung einer Tablette zur kontrollierten...

...398-10 ist, das in einer Menge von 10 Gew.-% vorliegt, und die porenbildenden Substanzen **Glycerin** , Wasser, Butanol und **Ethanol** sind, die in Mengen von 2, 2,8, 12,4 bzw. 22 Gew.-% vorliegen. ...
...CLAIMS ou plusieurs membranes asymetriques.
2. Dispositif suivant la revendication 1, dans lequel la membrane est **permeable** et est non perforee ou perforee.
3. Dispositif suivant la revendication 1, dans lequel la membrane est semi- **permeable** et non perforee.
4. Dispositif suivant la revendication 2 ou la revendication 3, dans lequel...

...la revendication 9, dans lequel la substance est un agent abaissant le taux sanguin de **glucose** .
17. Dispositif suivant la revendication 16, dans lequel la substance est le glipizide.
18. Dispositif...

...une quantite de 15 % en poids et les substances porogenes consistent en formamide, acide acetique, **glycerol** , un alcanol ayant 1 a 4 atomes de carbone, acetate de sodium, une solution aqueuse...

...ou polyvinylpyrrolidone.
24. Procede suivant la revendication 23, dans lequel la substance porogene est l' **ethanol** , present en une quantite de 30 % en poids.
25. Procede suivant la revendication 23, dans lequel la substance porogene est le **glycerol** , present en une quantite de 10 % en poids.

26. Procede suivant la revendication 21, comprenant...

...une quantite de 15 % en poids et les substances porogenes consistent en formamide, acide acetique, **glycerol** , un alcanol ayant 1 a 4 atomes de carbone, acetate de sodium, une solution aqueuse...

...ou polyvinylpyrrolidone.
28. Procede suivant la revendication 27, dans lequel la substance porogene est l' **ethanol** , present en une quantite de 30 % en poids.
29. Procede suivant la revendication 20, qui...

...10 present en une quantite de 15 % en poids,et les substances porogenes consistent en **glycerol** , eau, butanol et **ethanol** presentes respectivement en des quantites de 1,9, 2,7, 11,7 et 21,7...une quantite de 16 % en poids et la substance porogene consiste en formamide, acide acetique, **glycerol** , un alcanol ayant 1 a 4 atomes de carbone, acetate de sodium, une solution aqueuse...

...ou polyvinylpyrrolidone.
36. Procede suivant la revendication 35, dans lequel les substances porogenes consistent en **ethanol** et **glycerol** presents respectivement en des quantites de 28 et 8 % en poids.
37. Procede suivant la revendication 35, dans lequel la substance porogene est le **glycerol** , present en une quantite de 10 % en poids.

38. Procede de preparation de perles pour...

...lequel la substance porogene, qui represente 38 % en poids de la solution totale, consiste en **ethanol** , butanol, eau et **glycerol** presents, respectivement en des quantites de 57, 31, 7 et 5 % en poids, et l...

...10 present en une quantite de 15 % en poids et la substance porogene est l' **ethanol** present en une quantite de 33 % en poids.

46. Dispositif sous forme de capsule pour...

...ou plusieurs membranes asymetriques.

47. Dispositif suivant la revendication 46, dans lequel la membrane est **permeable** et perforee ou non perforee.

48. Dispositif suivant la revendication 47, dans lequel la liberation...

...une quantite de 16 % en poids et la substance porogene consiste en formamide, acide acetique, **glycerol** , un alcanol ayant 1 a 4 atomes de carbone, acetate de sodium, une solution aqueuse...

...ou polyvinylpyrrolidone.

53. Procede suivant la revendication 52, dans lequel les substances porogenes consistent en **ethanol** et **glycerol** presents respectivement en ...en poids.

54. Procede suivant la revendication 52, dans lequel la substance porogene est le **glycerol** , present en une quantite de 10 % en poids.

55. Procede de preparation d'un dispositif...

...membranes asymetriques.

58. Procede suivant la revendication 57, dans lequel la substance porogene est l' **ethanol** et l'ester de cellulose est l'acetate de cellulose 398-10.

59. Procede de...

...10 present en une quantite de 10 % en poids et les substances porogenes consistent en **glycerol** , eau, butanol et **ethanol** presents respectivement en des quantites de 2, 2,8, 12,4 et 22 % en poids.
...

33/5,K/4 (Item 4 from file: 348)
DIALOG(R)File 348:EUROPEAN PATENTS

00308823
Skin **permeation** enhancer **compositions using sucrose esters.**
Sukroseester enthaltende, die Hautpermeabilitat vergrossernde Zusammensetzungen.
Compositions augmentant la permeabilite **du derme utilisant les esters de sucrose.**
PATENT ASSIGNEE:
ALZA CORPORATION, (242661), 950 Page Mill Road P.O. Box 10950, Palo Alto California 94303-0802, (US), (applicant designated states: BE;CH;DE;ES;FR;GB;IT;LI;NL;SE)
INVENTOR:
Cheng, Yu-Ling, 20658 Celeste Circle, Cupertino, CA 95014, (US)
Gale, Robert M., 1276 Russell Avenue, Los Altos, CA 94022, (US)
Sugihara, Edna, 1479 Tyler Parkway, Mountain View, CA 94040, (US)
Sanders, Harold F., 751 B. Loma Verde Drive, Palo Alto, CA 94303, (US)
LEGAL REPRESENTATIVE:
Evans, David Charles et al (30461), F.J. CLEVELAND & COMPANY 40-43, Chancery Lane, London, WC2A 1JQ, (GB)
PATENT (CC, No, Kind, Date): EP 280413 A1 880831 (Basic)
EP 280413 B1 910703
APPLICATION (CC, No, Date): EP 88300772 880129;
PRIORITY (CC, No, Date): US 19442 870226
DESIGNATED STATES: BE; CH; DE; ES; FR; GB; IT; LI; NL; SE
INTERNATIONAL PATENT CLASS: A61L-015/00; A61K-047/00;
CITED PATENTS (EP A): EP 57462 A; DE 2241667 A; US 4568343 A
CITED REFERENCES (EP A):
CHEMICAL ABSTRACTS, vol. 90, no. 2, January 1979, page 363, abstract no. 12218y, Columbus, Ohio, US; K. DUCKOVA et al.: "Surfactants in suspension. II. Model experiments in vitro", & FARM. OBZ. 1977, 46(2), 59-68
CHEMICAL ABSTRACTS, vol. 85, no. 24, 13rd September 1976, page 308, abstract no. 182265a, Columbus, Ohio, US; & JP-A-76 92 802 (DAIICHI KOGYO SEIYAKU CO., LTD.) 13-02-1975;

ABSTRACT EP 280413 A1
A method for **enhancing** the transdermal flux of a transdermal deliverable drug through intact **skin** is described in which the drug is delivered simultaneously with sucrose monolaurate or a mixture of sucrose esters of coconut fatty acids, which is predominantly sucrose monolaurate. Preferred embodiments of therapeutic systems for delivering the drug and the sucrose ester employ a matrix containing drug at a concentration above saturation.
ABSTRACT WORD COUNT: 69

LEGAL STATUS (Type, Pub Date, Kind, Text):
Application: 880831 A1 Published application (A1with Search Report ;A2without Search Report)
Examination: 890412 A1 Date of filing of request for examination: 890201
Examination: 891227 A1 Date of despatch of first examination report: 891115
Grant: 910703 B1 Granted patent
Oppn None: 920624 B1 No opposition filed
LANGUAGE (Publication,Procedural,Application): English; English; English
FULLTEXT AVAILABILITY:
Available Text Language Update Word Count
CLAIMS B (English) EPBBF1 382

CLAIMS B	(German)	EPBBF1	373
CLAIMS B	(French)	EPBBF1	418
SPEC B	(English)	EPBBF1	2510
Total word count - document A			0
Total word count - document B			3683
Total word count - documents A + B			3683

Skin **permeation** enhancer **compositions using sucrose esters.**
Compositions augmentant la permeabilite **du derme utilisant les esters de sucrose.**

...ABSTRACT A1
A method for **enhancing** the transdermal flux of a transdermal deliverable drug through intact **skin** is described in which the drug is delivered simultaneously with sucrose monolaurate or a mixture...

...SPECIFICATION B1
This invention **relates** to the transdermal delivery of drugs or other biologically active agents and more particularly to novel methods and compositions for **enhancing** the **permeability** of **skin** or other **body** surfaces **to** biologically **active** agents.
The transdermal route of parenteral delivery of drugs provides many advantages and transdermal systems...

...would appear to be ideal candidates for transdermal delivery are found to have such low **permeability** through intact **skin** that they cannot **be** delivered at **therapeutically** effective rates from reasonably sized systems. In an effort to **increase skin permeability** it has been proposed **to pretreat the skin** with various chemicals or to concurrently **deliver** the drug in the presence of a permeation **enhancer** . Various materials have been suggested for **this** purpose as described in U.S. Patent Nos. 4,299,826; 4,343,798; 4...

...919-921). EP-A-0,057,462 discloses the use of a sucrose fatty acid **ester** to assist the uptake of elastase in the intestine following **oral administration** .
Chemical Abstract vol 90, number 2, January 1979, page 363, No. 12218y reports upon the use...

...semipermeable membrane. Neither relate to transdermal administration per se.
To be considered useful a permeation **enhancer** should possess certain characteristics in addition to its ability to **enhance** the **permeability** of at least one and preferably a large number of drugs. These characteristics include being non-toxic, non-irritating on prolonged exposure **and** under occlusion, and non-sensitizing on repeated exposure. Preferably it should also be odourless and...

...transdermal administration of a pharmaceutically effective amount of an active agent capable of permeation through **skin** and, either separately or admixed therewith, a permeation **enhancer** selected from sucrose monolaurate and mixtures of sucrose esters of coconut fatty acids.
According to...

...an impermeable backing;
characterised in that said reservoir comprises a pharmaceutically effective amount of an **active** agent **capable** of permeation through **skin** , and either separately or admixed therewith, a permeation **enhancer** selected from sucrose monolaurate and **mixtures** of sucrose esters of coconut fatty acids.

As noted above, the preferred sucrose ester is...

...that the C(sub 1)(sub 2) ester is most useful.

For the sucrose esters, **the** C(sub 1)(sub 2) is sucrose monolaurate. Alternatively, instead of using SML alone, mixtures...

...available source of one such SML predominating mixture is SUCROSE MONOCOCOATE, commercially available from Croda, **Inc** . (New **Jersey**), which is an ester mixture with C(sub 1)(sub 2) predominating.

It is accordingly an object **of** our invention to **increase** the **permeability** of **skin** of animals and humans and more particularly of human **skin** , to the transport of drugs and other beneficial agents by the concurrent application of the...

...is another object of our invention to provide compositions of matter for application to the **skin** which comprise SML and a **transdermally** deliverable drug or beneficial agent.

It **is** **another** object of our invention to provide transdermal therapeutic systems for the concurrent delivery of SML and a drug or **beneficial** agent.

According to the present invention we have discovered that SML **can** be used **to** **enhance** the **permeability** to drugs and **other** beneficial agents of body surfaces generally and, more particularly, to **enhance** the transdermal **permeability** of a multiplicity of drugs useful in the treatment of a wide variety of conditions and indications. As used **herein** the term "drug" relates to a biologically active agent, compound or composition of matter which is administered **for** the purpose of providing some beneficial or therapeutic effect. As used herein the term "transdermal" delivery relates to the delivery of a drug by passage through intact **skin** into the vascularized layers below the **stratum** **corneum** for absorption by the blood stream. Thus transdermal delivery is distinguished from topical application to the surface of intact **skin** for topical treatment or to application to open wounds or to **skin** lacking the **stratum** **corneum** such as burned or abraded **skin** . As used herein the term "SML" relates to sucrose monolaurate alone or to a mixture of sucrose esters of coconut fatty **acids** , with sucrose monolaurate predominating.

According to the present invention a **permeation** **enhancing** sucrose ester and the biologically active agent (drug) to be delivered are placed in drug and permeation **enhancer** transmitting relationship **to** the appropriate body surface, preferably **in** a carrier therefor, and maintained in place for the desired period of time. The drug and SML are typically dispersed together within a **physiologically** compatible matrix or carrier as more fully described below which may be applied directly to...

...in addition to its known low toxicity and colourless and odourless nature, does not sensitize **skin** on repeated exposure. Further, SML can be applied to the **skin** in compositions that do not produce irritation even on occlusion and repeated application to the same site and is capable of **enhancing** drug flux without producing objectionable **skin** sensations.

SML has utility in connection **with** the delivery of drugs within the broad class normally delivered through body surfaces and membranes, including **skin** . In general, this includes therapeutic agents in all of the major therapeutic areas including, but...

...such as antibiotics and antiviral agents, analgestics and analgestic combinations, anorexics, anthemidines, antiarthritics, antiasthmatic agents, **anticonvulsants** , antidepressants, antidiabetic agents,

antidiarrheals, antihistamines, anti-inflammatory agents, antimigraine preparations, antimotion sickness, antinauseants, antineoplastics, antiparkinsonism...

...central nervous system stimulants, cough and cold preparations, decongestants, diagnostics, hormones, hypnotics, immunosuppressives, muscle relaxants, **parasympatholytics** , parasympathomimetics, psychostimulants, sedatives and tranquilizers.

We have demonstrated the utility of SML as a permeation **enhancer** for a large number of dissimilar drugs within these classes, such as estradiol, hydrocortisone, progesterone...

...Additionally, we believe it to be applicable to an even larger number of such drugs **including** , by way of example and not for purposes of limitation; scopolamine, isosorbide dinitrate, **nitroglycerin** , clonidine, **cortisone** , theophylline, phenylephrine, **terbutaline** , ephedrine, narcotine, quinidine, estradiol diacetate, pilocarpine, furosemide, tetracycline, insuline, chlorpheniramine, sulfathiazides, propranolol, testosterone, norgestrel, lidocaine, morphinone, dihydrocodeine, dihydromorphine, oxycodone, hydrocodone, **codeine** , norcodeine, hydromorphine, normophine, norlevorphanol, dihydrothebaine, bromocryptine, guanabenz, salbutamol, oxprenolol, tetracaine, dibucaine, altenolol, pindolol and timolol...

...as to other drugs not specifically noted herein.

The effect of SML as a permeation **enhancer** for other drugs not specifically set forth herein may be readily determined by a worker...
...by in vivo measurements of blood or urine levels for example.

SML has a permeation **enhancing** effect on the transport of **drugs** through the **skin** . Because **skin** is one of the most effective of the **body** 's barriers to permeation foreign substances, the effect of SML on **skin** permeation makes it extremely useful in transdermal drug delivery.

Following is a description by way of example **only** and with reference to the accompanying drawings of methods of carrying the invention into effect...

...transdermal therapeutic system 1 according to this invention is shown which comprises a drug/permeation **enhancer** reservoir 2 in the form **of** a matrix containing the drug and permeation **enhancer** . The reservoir 2 is covered by an **impermeable** backing 3 which is preferably sized slightly larger in circumference than reservoir 2. Means 4 for maintaining the system on the **skin** may either be fabricated together with or provided separately from the remaining elements of the...

...2 to provide a peripheral area around reservoir 2 free of the sucrose ester permeation **enhancer** , to prevent adverse interaction between the adhesive in the overlay 4 and any of the **enhancer** which may seep from under the base of the reservoir 2 in use. A strippable...
...base. Suitable matrices or carriers are described in the above identified patents, and include, without **limitation** , natural and synthetic rubbers such as polybutylene, polyisobutylene, polybutadiene, polyethylene, styrenebutadiene, copolymers, polyisoprene, **polyurethane** , ethylene/propylene copolymers, polyalkylacrylate polymers, copolyesters, ethylene/acrylic copolymers, silicones and butadiene/acrylonitrile copolymers for example and other polymers such as the **ethylene** vinylacetate (EVA) polymers described in U.S. Patent No. 4,144,317 (which is incorporated herein by reference), for example, gelled or **thickened** mineral oil, petroleum jelly and various aqueous gels and hydrophilic polymers. Typically the drug is...

...the matrix or carrier at a concentration in excess of saturation, the amount of the **excess** being a function of the intended useful life of the system. The drug, however, may be **present** at initial levels below saturation without departing from this invention. The **enhancer** is preferably dispersed through the matrix at a concentration sufficient to provide permeation **enhancing** concentrations of SML in **the** reservoir throughout the anticipated administration time, but below irritability concentration.

In addition to the drug and permeation **enhancer** , which are essential to the invention, the matrix may also contain other materials such as dyes, pigments, inert fillers or other permeation **enhancers** , excipients and **conventional** components of pharmaceutical products or transdermal therapeutic systems as known to the art.

Referring now to Figure 2 another embodiment of this **invention** is shown in place upon the **skin** 17 of a patient. In this embodiment the transdermal therapeutic system 10 comprises a multilaminate drug/ **enhancer** reservoir 11 having at **least** two zones 12 and 14. Zone 12 consists of a drug reservoir substantially as described with respect to Figure 1. Zone 14 comprises a permeation **enhancer reservoir** which is preferably made from **substantially** the same matrix as used to form zone 12 and which is substantially free of...

...membrane 13 for controlling the release rate of the SML from zone 12 to the **skin** may also be utilized between zones 12 and 14 if desired. Suitable rate-controlling **membranes** may be formed from polymers having a **permeability** to SML lower than that of zone **12** .

An advantage of the system described in Figure 2 is that the drug loaded zone 12 is concentrated at the **skin** surface rather than throughout the entire mass of the reservoir. This functions to reduce the amount of drug in the system while maintaining an adequate permeation **enhancer** supply.

Superimposed over the drug/ **enhancer** reservoir 11 is an impermeable backing 15 and adhesive overlay 16 as described above with...

...to Figure 1. In addition, a strippable release liner (not shown) would preferably be provided **on** the system **prior** to use as described with respect to Figure 1 and removed prior to application to the **skin** 17.

With both Figures 1 and 2, the adhesive overlays can **be** eliminated if the **skin** contacting layer can be made adhesive. Use of such an **in** -line contact adhesive would mainly be limited by the compatibility of the adhesive with the...

...can be fully enclosed in a pouch or pocket between the impermeable backing and a **permeable** or microporous **skin** contacting membrane as known to the art from U.S. Patent No. 4,379,454, noted above, for example. Although the invention is most useful with drugs whose **permeability** is too low for therapeutic effects to be obtained in the absence of an **enhancer** ; its use with systems employing drug rate controlling membranes such as disclosed in U.S. Patent No. 3,598,122 and 3, **598** ,123 noted above is also contemplated.

EXAMPLE 1

A transdermal therapeutic system as described with...

...2) patch. Measurement of the progesterone blood level after an 8 hour period indicated an **increase** in progesterone of 40 ng/dl.

EXAMPLE II

A transdermal therapeutic system for administration of...

...a control sample (25% hydromorphone and 75% EVA 40), in the following table: (see image **in** original document)

EXAMPLE III

A transdermal therapeutic system for administration of levorphanol was formulated from...

...Measurement of the plasma progesterone and estradiol levels after a 24 hour period indicated an **increase** in progesterone of 44 ng/dl and in estradiol of 0.8 ng/dl.

Having...

...CLAIMS transdermal administration of a pharmaceutically effective amount of an active agent capable of permeation through **skin** and, either separately or admixed therewith, a permeation **enhancer** selected from sucrose monolaurate and mixtures of sucrose esters of coconut fatty acids.

2. The use as claimed in claim 1 characterised **in** that said agent and said **enhancer** are dispersed within a reservoir (2.11) therefor.

3. The use as claimed in claim...

...saturation concentration in the reservoir (2.11).

4. The use as claimed in any preceding **claim** characterised by an occlusive backing behind the **skin** distal surface of said reservoir (2.11) and

means (14.10) for maintaining said reservoir (2.11) in agent and permeation **enhancer** transferring relationship **to** intact **skin** (17).

5. **The** use as claimed in any preceding claim characterised in that said agent and said permeation **enhancer** are **contained** within a single reservoir means (2).

6. The use as claimed in any one of claims 1 to 5 characterised in that said agent and said permeation **enhancer** **are** contained within separate reservoir means (12.14).

7. The use as claimed in claim 6...

...said reservoir comprises a pharmaceutically effective amount of an active agent capable of permeation through **skin** , and either separately or admixed therewith, a permeation **enhancer** selected from sucrose monolaurate and mixtures of sucrose esters of coconut fatty acids.

9. A system according to claim 8 characterised in that said agent and said **enhancer** are dispersed within single reservoir 2.

10. A therapeutic system according to claim 8 characterised in that said agent and said permeation **enhancer** are contained within separate reservoir means (12.14).

11. A system according to any of...

...according to any of claims 8 to 11 characterised by an occlusive backing behind the **skin** distal surface of said reservoir (2.11), and means (14, 16) for maintaining said reservoir (2.11) in agent and permeation **enhancer** transferring relationship to intact **skin** (14). ...

...CLAIMS capable de passage a travers la peau et, separement ou melange avec elle, d'un **ameliorateur** de penetration choisi parmi le monolaurate de saccharose et les melanges d'esters de saccharose...

...coco.

2. Utilisation selon la revendication 1, caracterisee en ce que ledit agent et ledit **ameliorateur** sont disperses dans un reservoir (2.11) a cet effet.

3. Utilisation selon la revendication...

...pour maintenir ledit reservoir (2.11) dans une relation de transfert d'agent et d' **ameliorateur** de penetration a la peau intacte (17).

5. Utilisation selon l'une quelconque des revendications precedentes, caracterisee en ce que ledit agent et ledit **ameliorateur** de penetration sont contenus dans un seul moyen de reservoir (2).

6. Utilisation selon l'une quelconque des revendications 1 a 5, caracterise en ce que ledit agent et ledit **ameliorateur** de penetration sont contenus dans des moyens de reservoirs separes (12.14).

7. Utilisation selon...

...actif capable de penetration a travers la peau et, separement ou melange avec lui, un **ameliorateur** de penetration choisi parmi le monolaurate de saccharose et les melanges d'esters de saccharose...

...coco.

9. Systeme selon la revendication 8, caracterise en ce que ledit agent et ledit **ameliorateur** sont disperses dans un seul reservoir (2).

10. Systeme therapeutique selon la revendication 8, caracterise en ce que ledit agent et ledit **ameliorateur** de penetration sont contenus dans des moyens de reservoir separes (12.14).

11. Systeme selon...

...pour maintenir ledit reservoir (2.11) dans une relation de transfert d'agent et d' **ameliorateur** de penetration a la peau intacte (14).

...

33/5,K/5 (Item 5 from file: 348)
DIALOG(R)File 348:EUROPEAN PATENTS

00223314
Medical device for pulsatile transdermal delivery of biologically active agents.
Medizinische Einrichtung zur pulsatilen transdermalen Verabreichung von biologisch aktiven Wirkstoffen.
Dispositif medical pour l'administration pulsatile transdermique d'agents a activite biologique.
PATENT ASSIGNEE:
ALZA CORPORATION, (242660), 950 Page Mill Road P.O. Box 10950, Palo Alto California 94303-0802, (US), (applicant designated states: AT;BE;CH;DE;ES;FR;GB;GR;IT;LI;LU;NL;SE)
INVENTOR:
Gale, Robert M., 1276 Russell Avenue, Los Altos California 94022, (US)
Berggren, Randall G., 841 Polaris Way, Livermore California 94550, (US)
LEGAL REPRESENTATIVE:
Evans, David Charles et al (30461), F.J. CLEVELAND & COMPANY 40-43, Chancery Lane, London, WC2A 1JQ, (GB)
PATENT (CC, No, Kind, Date): EP 227252 A2 870701 (Basic)
EP 227252 A3 890405
EP 227252 B1 910918
APPLICATION (CC, No, Date): EP 86308248 861023;
PRIORITY (CC, No, Date): US 792941 851030
DESIGNATED STATES: AT; BE; CH; DE; ES; FR; GB; GR; IT; LI; LU; NL; SE
INTERNATIONAL PATENT CLASS: **A61M-037/00**
CITED PATENTS (EP A): US 4379454 A; GB 2135880 A

ABSTRACT EP 227252 A2
Medical device for pulsatile transdermal delivery of biologically active agents.
The present invention relates to A medical device for the pulsatile administration of a drug through intact **skin** at a first steady state flux during a first delivery period and a second steady state flux during a second delivery period, said first flux being substantially higher than said second flux; said first and second delivery periods comprising a substantial portion of a predetermined administration period, characterised in that said device comprises:
a) a reservoir of said drug containing an amount of drug sufficient to adminster drug at said first and second steady state fluxes throughout said administration period;
b) a reservoir of a **skin** permeation **enhancer** for said drug; said reservoir containing an amount of said permeation **enhancer** sufficient to **permit** administration of said drug at said first flux only through said first delivery period; and
c) means for maintaining said device on the **skin** in drug and permeation **enhancer** transferring relationship thereto.
ABSTRACT WORD COUNT: 165

LEGAL STATUS (Type, Pub Date, Kind, Text):
Application: 870701 A2 Published application (A1with Search Report ;A2without Search Report)
Search Report: 890405 A3 Separate publication of the European or International search report
Examination: 891108 A2 Date of filing of request for examination: 890906
*Assignee: 901017 A2 Applicant (name, address) (change)
Examination: 910130 A2 Date of despatch of first examination report:

901213
Grant: 910918 B1 Granted patent
Oppn None: 920909 B1 No opposition filed
LANGUAGE (Publication,Procedural,Application): English; English; English
FULLTEXT AVAILABILITY:

Available Text	Language	Update	Word Count
CLAIMS B	(English)	EPBBF1	853
CLAIMS B	(German)	EPBBF1	701
CLAIMS B	(French)	EPBBF1	921
SPEC B	(English)	EPBBF1	5850
Total word count - document A			0
Total word count - document B			8325
Total word count - documents A + B			8325

INTERNATIONAL PATENT CLASS: **A61M-037/00**

...ABSTRACT invention relates to A medical device for the pulsatile administration of a drug through intact **skin** at a first steady state flux during a first delivery period and a second steady...

....first and second steady state fluxes throughout said administration period;
b) a reservoir of a **skin** permeation **enhancer** for said drug; said reservoir containing an amount of said permeation **enhancer** sufficient to **permit** administration of said drug at said first flux only through said first delivery period; and
c) means for maintaining said device on the **skin** in drug and permeation **enhancer** transferring relationship thereto.

...SPECIFICATION delivering biologically active agents (hereinafter referred to generally as "drugs") to the body through intact **skin** and more particularly for the pulsatile delivery of drugs at at least two different predetermined...

...preamble of claim 1.
BACKGROUND OF THE INVENTION
Medical devices that deliver drugs through the **skin** for absorption into the body have been known for some time. For example, U.S...

...fabric backing layer. This type of device delivers a varying amount of drug to the **skin** and the rate of absorption is determined by the release rate of drug from the device, which decreases as a function of time of application, and the **permeability** of the **skin** at the administration site. In order to transdermally deliver drugs having a relatively narrow therapeutic...

...and includes means for metering the rate at which the drug is released to the **skin** . Other representative system controlled transdermal delivery devices are described in U.S. Patents 3,797...

...latter of which teaches controlling the rate at which a drug is absorbed through the **skin** by controlling the rate at which a permeation **enhancer** for the drug is delivered to the **skin** . (All of the aforementioned U.S. patents are incorporated herein by reference.) In addition, Black...

...910-922; and Cooney, Advances in Biomedical Engineering, Part 1, Chapter 6, "Drug Permeation Through **Skin** : Controlled Delivery for Topical Systemic Therapy", Marcel Dekker, Inc., New York and Basel 1980, pp...

...have a relatively long lag time between the time the device is applied to the **skin** and the time that therapeutic levels are achieved in the blood. This is because the...

...agent from the device into the bloodstream is a diffusional process and requires the necessary **concentration gradient** to be established between the device and the internal surfaces of the **skin** . Attempts to decrease the lag time have been proposed and include a "pulse" dosage of the drug in the adhesive layer in contact with the **skin** in order to initially saturate the **skin** binding sites so that delivery into the systemic circulation can begin sooner and treatment of the **skin** with permeation **enhancers** , either prior to administration of the device or concurrently with the drug administration. (See for...

...throughout the entire administration the higher or the lower level throughout the entire administration period. **Nitroglycerin** , for example, could be delivered in such a regime.

It is therefore a primary object...a device is particularly suitable for delivering drugs which are capable of permeating through normal **skin** at rates which produce therapeutic doses from reasonably sized devices without the use of permeation **enhancers** . It also contemplated that the device could be employed to deliver drugs which are less **permeable** if the **skin** at the delivery site is pretreated to **increase** its **permeability** by perforating, stripping, abrading or chemically treating the **stratum corneum** .

It is another object of this invention to provide a pulsatile transdermal drug delivery device...

...drawings, wherein:

Figure 1 is a plot of theoretical in vitro release rates through cadaver **skin** into an infinite sink of typical transdermal delivery devices of the prior art and of...

...according to this invention.;

Figure 6 is a plot of in vitro drug flux through **skin** as a function of permeation **enhancer** flux through **skin** ;

Figure 7 is a plot of in vitro **nitroglycerin** and **ethanol** fluxes through cadaver **skin** into an infinite sink as a function of time according to this invention; and

Figure 8 is a plot of **nitroglycerin** plasma levels as a function of time for an embodiment of this invention.

DESCRIPTION OF...

...running from t(sub 0) to t(sub 1) in which there is a rapid **increase** of the rate of release into an infinite sink through human cadaver **skin** from the device which results from the initial loading of the drug at the surface in contact with the **skin** . After this initial transient period has expired, the uncontrolled devices such as disclosed in U...

...from t-t(sub 2) in which the concentration of the agent is sufficient to **permit** the delivery rate to be limited by the **skin** until the concentration of the drug in the device drops at t(sub 2) to...

...sub 1) and t(sub 2) is determined by the initial drug loading and the **permeability** of the system itself.

When a rate controlled device is used a pattern such as...

...device is typically designed to release agent at a rate lower than that obtainable through **skin** of average **permeability** and to contain sufficient drug such that unit activity (saturation concentration) is

maintained throughout the...

...limited by the time during which a system can be maintained in contact with the **skin** without producing undesirable effects from occlusion or irritation. When adhesive systems are utilized it is...

...practical to transdermally deliver a drug beyond the 7 day period in which the human **skin** surface layer is replaced from the underlying tissue.

The steady-state portion of the administration...does not necessarily parallel the release rate curve. This is because of factors such as **skin** binding, and also because of the competing rates of drug delivery into the blood and...

...clearance from the blood as a result of metabolic action on the drug in the **skin** or body.

Figures 2-5 disclose embodiments of medical devices according to this invention which...

...will be more specifically described below. Thus, for example, Figure 2 illustrates a self-adhering **skin** patch 11 designed to be placed on unbroken **skin** 12. Device 11 is a laminate that consists of four layers, an impermeable top backing layer 13, a drug/permeation **enhancer** reservoir layer 14, a rate controlling membrane layer 15, and a contact adhesive layer 16...

...Reservoir layer 14 is immediately below backing 13. It contains supplies of both the permeation **enhancer** and the drug. Rate controlling membrane layer 15, the next layer of the device may be made of a dense or microporous polymer film that has the requisite **permeability** to the drug and permeation **enhancer** . It is the element of patch 11 that controls the rate at which the permeation **enhancer** and drug are delivered to the **skin** . The respective fluxes of the drug and **enhancer** through layer 15 will depend upon the thickness of the layer, its diffusion coefficients relative to the drug and the **enhancer** , and the concentration and loading of permeation **enhancer** in the reservoir. The diffusion coefficients of the layer 15 for a particular drug and **enhancer** may be determined by standard techniques. Examples of the types of polymer films that may...

...It is one means by which device 11 may be affixed to the area of **skin** to be treated. Its composition and thickness are normally such that it does not constitute a significant permeation barrier to either the drug or the **enhancer** , and normally it will be substantially more **permeable** to the drug **enhancer** than layer 15. During the time interval between the manufacture and the use of device 11, layer 16 may absorb **enhancer** and drug in amounts that will depend upon the composition, solubility of the components in...

...length of the time interval. If the interval is quite long, layer 16 will absorb **enhancer** and the drug until it is saturated with both. Contact adhesive compositions that may be...

...a protective undercoating layer made from materials that are substantially impermeable to the drug, the **enhancer** , and any other components of layer 16. The same materials that are used to make...

...adhesive 16 and discarded. Device 11 is then applied to a relatively nonhairy area of **skin** 12 that is substantially free of wrinkles, creases, or folds. Various locations on the torso...

...provide suitable sites for the bandage. As indicated above, once it is placed on the **skin** the bandage will begin co-administering drug and permeation **enhancer** to the wearer.

In order to obtain the pulsatile drug delivery pattern desired according to...

...now to Figures 6 and 7 typical plots for the relationship between drug flux through **skin** and permeation **enhancer** flux through **skin** are shown. It can be seen from Figure 6 that at permeation **enhancer** fluxes in the range of O to A there is a more or less direct relationship between **enhancer** flux and drug flux, with the drug flux **increasing** from the level X, at which the drug permeates through untreated **skin** , to level Y. At **enhancer** fluxes greater than A and up to level B, at which irreversible changes are created in the **skin** , there may, in many cases, be no significant **increase** in drug delivery rate with **enhancer** flux.

A representative pulsatile drug delivery device according to this invention therefore would be designed...

...controlling membrane 15 may either control the delivery rate of the drug or the permeation **enhancer** . Thus for example, if membrane 15 were to control the **enhancer** delivery rate its characteristics would be selected such that the **enhancer** flux through **skin** would be at level C as shown in Figures 6 and 7. If, on the other hand, membrane 15 were selected to control the drug flux; the **enhancer** would be delivered in substantial excess such that the **enhancer** flux through **skin** during the initial steady state period is in excess of C but less than B. The membrane 15, in that case, would be selected to reduce the drug flux through **skin** down to level Z. At the commencement of the second and lower steady state delivery rate regime the **enhancer** flux drops rapidly below level C, causing the the drug flux through **skin** to drop to level X, the rate at which the drug permeates through substantially untreated **skin** or the level X' a slightly higher level equivalent to the rate at which drug permeates through **skin** which has been previously treated with a permeation **enhancer** but in the absence of continuous permeation **enhancer** delivery. Level X' may be slightly higher than X due to some small, transient and non-damaging changes in the properties of the **skin** .

In order to accomplish the desired pulsatile delivery according to this invention the loadings of the drug and the permeation **enhancer** are critical. The loading of the drug must be at least equal to the total...

...all of the time period t(sub 0)-t(sub 3) The loading of permeation **enhancer** , however, can be no greater than that required to deliver **enhancer** within the selected flux range only until the expiration of the high steady state delivery...

...sub 2). At the termination of the high rate regime, the activity of the permeation **enhancer** in the reservoir should be depleted so that the **enhancer** flux rapidly drops below level C.

This invention is applicable to a wide variety of drugs and permeation **enhancers** , within certain constraints imposed by the nature of the invention. For example, a drug to be usable according to this invention without pretreatment of the **skin** would have to have sufficient **permeability** through normal **skin** to produce a therapeutic effect when administered at flux level X or X'. Similarly, the permeation **enhancer** would have to be of the type that does not produce substantial changes in the properties of the **skin** that are not rapidly reversible when the

permeation **enhancer** is removed. Suitable permeation **enhancers** will vary from drug to drug but include **ethanol** , n-decylmethyl sulfoxide (nDMS), dimethyl lauramide, and polyethylene glycol monolaurate (PEGML), for example. Unsuitable permeation **enhancers** are of the type that appear to produce non-transient changes in the **skin** which include dimethylsulfoxide, for example.

Referring now to Figure 3, another embodiment of the invention, generally designated 17, is shown in which the drug and **enhancer** are stored in separate reservoirs. Device 17 is composed of four layers, a backing layer 18, a permeation **enhancer** reservoir layer 19, a rate controlling membrane layer 22 and a drug reservoir-contact adhesive...

...function to layer 13 of embodiment 11. Layer 19 contains the supply of percutaneous absorption **enhancer** . As in Figure 1 the loading of **enhancer** in layer 19 will depend on the rate and duration of **enhancer** administration required to achieve the desired pulsatile drug delivery. Layer 22 is the component of device 17 that controls the release rate of **enhancer** to the **skin** . In this regard it is structurally, compositionally and functionally similar to membrane 15 of embodiment 11. Because the drug does not pass through layer 22, layer 22 need not be **permeable** to the drug. Indeed it is preferred that it be substantially impermeable to the drug...

...in layer 23 at or above saturation from t(sub 0) - t(sub 3). This **permits** a unit activity source to be available for delivery throughout the entire administration period and...

...2, it is also possible to control the release rate of drug and deliver the **enhancer** in an uncontrolled manner. In that instance, layer 19 would be the drug reservoir, layer 22 would maintain drug flux at level Y and layer 23 would contain the **enhancer** at a loading such that the **enhancer** flux would drop rapidly below level C after t(sub 2).

Embodiments such as device 17 in which the drug and **enhancer** supplies are separate may be advantageous or necessary in instances where formulation or storage of the drug and **enhancer** in contact with each other is impractical or undesirable or where separation of the drug and **enhancer** make selection of the rate controlling membrane easier.

Figure 4 illustrates another embodiment, generally designated 25, in which the supplies of drug and **enhancer** are separate Device 25 is a laminate composed of two layers, a backing layer 26...

...11. Heterogeneous basal layer 27 is composed of a continuous matrix phase 28 in which **enhancer** -containing microcapsules 29 and drug 32 (represented by stippling in Figure 4) are dispersed. Continuous matrix phase 28 is a solid, semisolid or gel composition that is **permeable** to the **enhancer** and the drug. It preferably adheres to **skin** . If it does not, an adhesive overlay will have to be used to keep embodiment 25 in contact with the **skin** . The contact adhesive compositions that are used to make the contact adhesive layers of embodiment...

...as continuous matrix phase 28. Microcapsules 29 each consist of an inner core of permeation **enhancer** encapsulated by a rate controlling membrane. The membrane functions as membranes 15 and 22 and...

...15 and 22. Accordingly, the membrane on each microcapsule controls the rate at which the **enhancer** is released therefrom. The combined release of **enhancer** from all the microcapsules in turn defines the rate of release of **enhancer** from embodiment 25. As in the case of the other embodiments the loading of **enhancer** contained in layer 27 in microcapsule form will depend upon the required **enhancer** release rate and duration of the high delivery rate phase. Microcapsules 29 may be

made...

...given instance will depend upon the rate at which the drug is absorbed by the **skin** from layer 27 and the duration of therapy. The thickness and composition of continuous phase...

...should be such that it does not constitute a principal permeation barrier to either the **enhancer** or the drug. As with respect to the devices. Figures 2 and 3 the drug could be encapsulated in the microcapsules and the permeation **enhancer** dispersed in layer 27 with the same constraints as described with respect to Figures 2...

...device 33 are backing layer 34, a reservoir layer 35 that contains supplies of permeation **enhancer** and drug, a diffusion membrane layer 36, and a peripheral ring 37 of contact adhesive...

...the form of a peripheral ring rather than a continuous basal layer. Neither drug nor **enhancer** passes through ring 37 and it, therefore, need not be **permeable** to these compositions. Secondly, the basal surface from which drug and **enhancer** is transferred to the **skin** is defined by rate controlling membrane layer 36. Thirdly, the backing layer is not flat...

...contact adhesive.

The embodiments of Figures 2-5 may be designed to administer drug and **enhancer** at the rates required to achieve the desired pulsatile drug therapy. In order to determine the optimum rates for a given drug-**enhancer** combination it is necessary to determine the **permeability** of **skin** to the drug and the permeation **enhancer** and the relationship between the drug flux and **enhancer** flux through **skin** .

The following discussion will illustrate the techniques employed in designing pulsatile transdermal delivery devices according to this invention with respect to a transdermal drug delivery device for delivering **nitroglycerin** in a pulsatile mode. A high rate of approximately 80 (mu)g/cm(sup 2...

...of a 24 hour administration period were selected as targets and normal having the average **permeabilities** to **nitroglycerin** and **ethanol** of normal human **skin** were used as design criteria.

The steady state, in vivo drug input rate, Jnet, of an agent, such as a drug or permeation **enhancer** delivered through the **skin** from a transdermal delivery device is given by the following relationship: (see image in original...

...state flux of agent from the device directly into an infinite sink and J(sub(**skin**)) is the in vivo or in vitro steady state inherent flux of agent directly through **skin** from a unit activity source into an infinite sink, all units being expressed in (mu)g/cm(sup 2)/hr.

The **permeability** of normal human **skin** to NG, is in the range of about 10-50 (mu)g/cm(sup 2...

...be used to establish the J(sub(device)) (NG) in the absence of a permeation **enhancer** and the upper NG delivery rate of 80 (mu)g/cm(sup 2)/hr will determine the additional characteristics required for the initial phase. In order to **permit** the **skin** to primarily control the lower steady state rate, the J(sub(device)) (NG) must be substantially higher than J(sub(**skin**)) (NG). For example, application of Formula ...2)/hr.

To achieve the initial high in vivo drug fluxes contemplated herein, a permeation **enhancer** must be delivered in the initial phase at a flux

sufficient to **increase** the J(sub(net)) (NG) to about 80 (mu)g/cm(sup 2)/hr. **Ethanol** , within certain flux ranges produces a non-damaging, reversible effect on **skin** **permeability** , and is suitable for use as a NG permeation **enhancer** according to this invention. The delivery device of this example therefore should be designed to deliver **ethanol** at a flux sufficient to **increase** the NG **permeability** of the **skin** to a value no less than the J(sub(net)) of NG in the high initial phase and preferably substantially higher.

It has been determined that **ethanol** can reversibly **increase** the J(sub(**skin**)) (NG) for average **skin** to levels greater than 80 (mu)g/cm(sup 2)/hr if the J(sub(net)) of **ethanol** delivered through the **skin** is at least about 250 (mu)g/cm(sup 2)/hr and preferably higher but ...

...500 (mu)g/cm(sup 2)/hr, the level at which unacceptable and temporarily irreversible **skin** changes are observed. The **permeability** of average human **skin** to **ethanol** is in the range of about 1200 to 1500 (mu)g/cm(sup 2)/hr. Therefore the **ethanol** J(sub(device)) according to this invention is preferably in the range of about 300 to 750 (mu)g/cm(sup 2)/hr to obtain the average target **ethanol** J(sub(net)) of about 250-500 (mu)g/cm(sup 2)/hr. Ethylene vinyl...

...of 12-18% possess the necessary characteristics to maintain the fluxes of both NG and **ethanol** within the respective ranges required according to this invention.

It is also necessary that certain drug and **ethanol** loadings be initially present in the reservoir such that the delivery device will function to...

...at the selected rates throughout the selected portions of the 24 hour administration period, and **ethanol** at the desired rate only for the initial high delivery rate phase of about 10...

...The initial NG loading would normally be in excess of the minimum loading. The maximum **ethanol** loading per cm(sup 2) is determined by the **ethanol** flux required in the initial high delivery rate phase, the duration of the phase and the solubility of **ethanol** in its carrier. Because of the high **permeability** of **skin** to **ethanol** the desired fluxes can be obtained from sub-saturated sources having an activity less than 1. **Ethanol** fluxes within the selected ranges can be obtained if the initial loading of **ethanol** is sufficient to maintain the thermodynamic activity of **ethanol** above about 0.2 during the initial phase and thereafter drop below about 0.2...

...2), the time of commencement of the low NG administration rate phase.

A typical NG- **ethanol** reservoir composition according to this invention comprises a dispersant having a low solubility, below about 5 mg/gm, for NG and **ethanol** and having the NG and the **ethanol** dispersed therethrough. To facilitate dispersion the NG and **ethanol** would be absorbed on a suitable carrier such as lactose for NG and porous polypropylene or colloidal silicon dioxide for the **ethanol** , for example, as disclosed in copending U.S. patent application of Gale et al., Serial Number 06/730,714 filed May 3, 1985 for Transdermal Delivery System for Delivering **Nitroglycerin** at High Transdermal Fluxes.

The aforementioned patents and applications and U.S. Patent 4,144...

...medical fluid gelled with silica as the reservoir, colloidal silica or porous polypropylene as the **ethanol** absorbent and an EVA membrane having a minimum of 11% VA and preferably about 12...

...about 1-3 mils. The higher the VA content of the EVA, the greater the **permeability** to both NG and **ethanol** . The **ethanol** may be included as absolute alcohol although it is preferred, particularly from a cost standpoint to utilize the substantially less expensive aqueous USP 95% **ethanol** . More dilute **ethanol** solutions can be employed provided the **ethanol** activity is maintained above about 0.2 throughout the initial high delivery rate period and...

...devices according to the invention the following specific examples are provided.

EXAMPLE 1

A NG/ **ethanol** reservoir composition comprising a silicone medical fluid carrier gelled with silica, having NG on lactose uniformly dispersed therethrough and **ethanol** absorbed in a particulate carrier is fabricated by placing 5 kg of silicone medical fluid...

...from ARMAK Company is placed in a separate vessel and approximately 1100 grams of USP **ethanol** (95% **ethanol**) is added with stirring to produce an essentially dry, flowable powder which on visual observation appears to have absorbed substantially all of the **ethanol** . Five kg of **nitroglycerin** -lactose (10%wt **nitroglycerin**) and the **ethanol** loaded porous polypropylene are placed in the original high energy mixing vessel and mixed until a homogeneous blend is obtained. A pouching machine is used to pouch the NG- **ethanol** gel so formed between an impermeable backing member comprising a medium density polyethylene/aluminized polyester...

...formed from a 1.5 mil thick EVA (12% VA) membrane to produce NG and **ethanol** loadings of 2.6 mg/cm(sup 2) and 4.8 mg/cm(sup 2) respectively. Systems can be fabricated having NG/ **ethanol** releasing surface areas of varying sizes such as approximately 5 cm(sup 2), 10cm(sup...

...A transdermal therapeutic device was fabricated according to procedure of Example 1 except that the **ethanol** is absorbed on 200 grams of colloidal silicon dioxide. The performance will be substantially the...

...VA) film and with loadings of 5 mg NG/cm(sup 2) and 20 mg **ethanol** /cm(sup 2). The device will perform in a manner similar to that of Example...

...CLAIMS B1

1. A medical device (11) for the pulsatile administration of a drug through intact **skin** (12) at a first steady state flux during a first delivery period and a second...

...first and second fluxes throughout said administration period;

b) a reservoir of (14) of a **skin** permeation **enhancer** for said drug; and

c) means (16) for maintaining said device on the **skin** in drug and permeation **enhancer** transferring relationship thereto, characterized in that the second flux during the second delivery period is a steady state flux and in that the reservoir (14) of the **skin** permeation **enhancer** for the drug contains an amount of said permeation **enhancer** sufficient to **permit** administration of said drug at said first flux only through said first delivery period.

2...

...device (11) as claimed in claim 1 characterised in that said drug reservoir and permeation **enhancer** reservoir is a common reservoir (14) comprising drug and permeation **enhancer** dispersed within a carrier.

3. A device (11) as claimed in claim 1 or claim...

...characterised in that release rate controlling means (15) for one of said drug and permeation **enhancer** is disposed between the respective reservoir (14) and the **skin** (12).

4. A device (17) as claimed in claim 1 characterised in that said drug reservoir and said permeation **enhancer** reservoir are two separated reservoirs (23, 19), a release rate controlling means (22) controls the release rate of said permeation **enhancer** and is disposed between the permeation **enhancer** reservoir (19) and the drug reservoirs (23) in the flow path of permeation **enhancer** from said **enhancer** reservoir (19) to the **skin** .

5. A device (17) as claimed in any preceding claim characterised in that said drug reservoir (23) comprises the **skin** contacting surface of the device.

6. A device (17) as claimed in claim 5 characterised...

...adhesive and said drug reservoir (23) comprises the means for maintaining the device on the **skin** .

7. A device (11) as claimed in any preceding claim characterised in that said means for maintaining the device on the **skin** comprises a contact adhesive (16) on the **skin** contacting surface of the device.

8. A device as claimed in claim 1 characterised in that drug and permeation **enhancer** reservoirs are separated, a release rate controlling means controls the release rate of said drug during said first delivery period and is disposed between said drug reservoir and said **enhancer** reservoir in the path of drug flow from said drug reservoir to the **skin** .

9. A device as claimed in anyone of claims 3 to 7 characterised in that said release rate controlling means controls the rate of release of said permeation **enhancer** .

10. A device as claimed in any one of claims 3 and 8 characterised in...

...11. A device as claimed in any preceding claim characterised in that said drug is **permeable** through normal human **skin** at therapeutic fluxes.

12. A device as claimed in any preceding claim characterised in that...

...13. A device as claimed in any preceding claim characterised in that said drug is **nitroglycerin** and said permeation **enhancer** is **ethanol** .

14. A device as claimed in claim 13 characterised in that the release rate controlled means controls the release rate of **ethanol** ; said device being characterized by having a J device for **nitroglycerin** of at leaeans controls the release rate of **ethanol** ; said device being characterised by having a J device for **nitroglycerin** of at least about 28 (mu)g/cm(sup 2)/hr, a J device for **ethanol** in the range of 300-750 (mu)g/cm(sup 2) /hr, said **ethanol** reservoir containing that amount of **ethanol** required to **allow** the activity of the **ethanol** in the reservoir to drop below about 0.2 at the end of said first delivery period and said **nitroglycerin** reservoir containing sufficient **nitroglycerin** to supply **nitroglycerin** at said first and second steady state fluxes at least until the expiration of said...

...device as claimed in any one of claims 13 to 17 characterised in that said **nitroglycerin** reservoir and said **ethanol** reservoir comprises a common reservoir of **nitroglycerin** and **ethanol** in a carrier

having solubility for **nitroglycerin** and **ethanol** of no more than about 5 (mu)g/gm.

19. A device as claimed in...

...CLAIMS selon l'une quelconque des revendications precedentes, caracterise en ce que ledit medicament est la **nitroglycerine** et ledit activateur de penetration est l' **ethanol** .

14. Dispositif selon la revendications 13, caracterise en ce que le moyen de regulation de vitesse de liberation commande la vitesse de liberation de l' **ethanol** , ledit dispositif etant caracterise et, ce qu'il a u J(en indice(dispositif)) pour la **nitroglycerine** d'au moins environ 280 (mu)g/cm(sup 2)/heure, un J(en indice(dispositif)) pour l' **ethanol** dans un intervalle de 300-750 (mu)g/cm(sup 2)/heure, ledit reservoir d' **ethanol** contenant la quantite d' **ethanol** requise pour permettre a l'activite de l' **ethanol** dans le reservoir de baisser en dessous de 0,2 a la fin de ladite premiere periode d'administration, et ledit reservoir de **nitroglycerine** contenant suffisamment de **nitroglycerine** pour fournir la **nitroglycerine** auxdits premier et second flux constants au moins jusqu'a l'expiration de ladite periode...l'une quelconque des revendications 13 a 17, caracterise en ce que ledit reservoir de **nitroglycerine** et ledit reservoir d' **ethanol** comprennent un reservoir commun de **nitroglycerine** et d' **ethanol** dans un support ayant une solubilite pour la **nitroglycerine** et l' **ethanol** d'au plus environ 5 (mu)g/g.

19. Dispositif selon l'une quelconque des...

33/5,K/6 (Item 6 from file: 349)
DIALOG(R)File 349:PCT FULLTEXT

00309358
SCREENING METHODS FOR INTEGUMENTAL INFLAMMATION MODULATING AGENTS
PROCEDES DE CRIBLAGE DES AGENTS MODULATEURS DES INFLAMMATIONS TEGUMENTAIRES
Patent Applicant/Assignee:
DE NOVO CORPORATION,
MAK Vivien H W,
Inventor(s):
MAK Vivien H W,
Patent and Priority Information (Country, Number, Date):
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Detailed Description
Claims
Fulltext Word Count: 48932

English Abstract
The present invention provides a number of screening methods for evaluating compounds capable of suppressing cytokine production either in vitro or in vivo. The methods generally involve stimulating the production of a cytokine in a cell, exposing a portion of the cells to a putative cytokine modulating agent and determining subsequent levels of cytokine production in the cells. Additionally, the present invention provides certain compounds identified by this method.

French Abstract
La presente invention concerne plusieurs procedes d'evaluation par criblage in vitro ou in vivo de composes susceptibles de supprimer la production de cytokine. Les procedes consistent generalement en une stimulation de la production d'une cytokine d'une cellule, en l'exposition d'une partie des cellules a un agent dont on suppose qu'il peut moduler la production de cytokine, et en une determination des niveaux de production de cytokine dans les cellules. La presente invention concerne en outre certains composes identifies grace a ce procede.

Patent and Priority Information (Country, Number, Date):
Patent: ... **19951019**
Fulltext Availability:
Detailed Description
Claims
Publication Year: **1995**

Detailed Description
... useful as medicaments in the treatment of a variety of acute and chronic, systemic or **skin** conditions having an inflammatory and/or immunological component.

BACKGROUND OF THE INVENTION
Inflammation represents a...significant overlaps between the current understanding of the pathophysiology leading to the development of acute **skin** disorders and acute systemic inflammatory conditions like endotoxemia. In both scenarios, TNF production by hematopoietic...

...of more TNF receptors making TNF seminal in this disease pathogenesis. Similarly, there is an **increased** level of TNF in the intestinal mucosa (Olson, et al., J. Pediatric Gastroenterology and Nutrition...

...also mainstay anti-inflammatory agents but manifest significant adverse effects, such as inducing Cushingoid features, **skin** thinning, **increased** susceptibility to infection, and suppression of the hypothalamic-pituitary-adrenal axis. The use of other ...

...effects. Methods which suppress TNF production will find application not only in inflammation of the **skin** , but also in systemic inflammation.

Surprisingly, the present invention provides such methods of suppressing TNF...

...DRAWINGS
Figure 1 illustrates the ability of verapamil to suppress inflammation in TPA-treated mouse **skin** .

Figure 2 illustrates ...s1dn.

Figure 3 illustrates the ability of verapainil to suppress inflammation in DNCB-treated mouse **skin** .

Figure 4 illustrates the ability of amiloride to suppress inflammation in DNCB-treated mouse s1dn...

...in man.

Figure 6 illustrates the ability of verapamil. to suppress epidermal swelling in a **skin** inflammation model in man.

SUMMARY OF THE INVENTION
The present invention provides screening assays to...

...the inflammatory response.

In one embodiment, the present invention provides a method of screening for **skin** immune or inflammation modulating agents. In this method, keratinocytes are stimulated to produce at least...

...MHC Class H molecule. A portion of the keratinocytes are then exposed to a putative **skin** inflammation modulating agent, and a determination is made as to whether the putative agent is...
...or a benzothiazepinone. More preferably the calcium channel blocker will be administered as a specific **optical** isomer for those compounds having at least one **optical** center. The selection of the **optical** isomer for use in the present invention is such that an optimal modulation of TNF... limited to Retin-A.

In yet another embodiment, the present invention includes methods of modulating **skin** inflammatory response wherein an anti-inflammatory

preparation is applied to the **skin** .

In still another embodiment, the present invention includes methods for treating a non-allergic **skin** inflammatory condition in a mammal, wherein a TNF inhibitor is administered to a mammal displaying...

...determined.

The present invention also includes methods of modulating and treating inflammatory responses in the **skin** in which an electric field effective to modulate the production of cytoldnes in the sldn...

...In another embodiment, the electric field is applied to the sldn in conjunction with a **skin** inflammation modulating (suppressing or inducing) drug.

The present invention also provides methods for reducing sldn adverse reactions, sensitization and irritation associated with the application of a transdermal or **iontophoretic** delivery device, and/or other drugs to the sldn.

Still further, the present invention provides...

...for the treatment of ocular inflammation using TNF inhibitors and methods for the treatment of **skin** sensitization or irritation associated with the use of a cosmetic or **skin**0 care product.

DETAILED DESCRIPTION OF THE INVENTION
Table of Contents

I. Treatment of Superficial...

Claim
The term " **optical** center" or "chiral center" refers to a center, usually a carbon atom, which has four...

...chirality can be specified according to the Cahn-Ingold-Prelog system. In this system, each **optical** center can be defined as having an R- or an S-configuration. Accordingly, molecules which have at least one **optical** center are termed "chiral molecules." A molecule is chiral if no stable conformation can be superimposed on its mirror image. A molecule having at least one **optical** center can therefore exist as a racemic pair of enantiomers, each enantiomer rotating polarized **light** in equivalent but opposite direction. Each of these enantiomers can be termed (+)- or (+ depending upon whether polarized **light** is rotated in a clockwise or counter-clockwise direction, respectively. A racemic mixture, often termed a (+/-)-mixture, can be separated into its " **optical** isomers," namely the (+)-isomer and the (-)-isomer. Equivalent terms for the (+)-isomer and the (-)-isomer...

...inflammatory lesions or other abnormities upon examination of the patient. This would also represent an **improvement** or a successful treatment. Prevention of deterioration of the recipient's status is also included...morphological appearance comprising well-organized basal, spinous, and granular layers, and a coherent multi-layered **stratum corneum** . In addition, the normal or healthy epidermis comprises a terminally differentiated, stratified squamous **epithelium** with an undulating junction with the underlying dermal tissue. Normal or healthy **skin** further contains no signs of fluid retention, cellular infiltration, hyper- or hypoproliferation of any cell...

...and dermal dendrocytes. This appearance is documented in dermatological textbooks, for example, HISTOPATHOLOGY OF THE **SKIN** , Lever and Schaumburg-Lever (eds.), J.B. Lippincott Company (1991) and TExTBOOK OF DERMATOLOGY, Champion...

...eds.), 5th Ed. Blackwell Scientific Publications (1992), especially Chapter 3 "Anatomy and Organization of Human **Skin** "; PHYSIOLOGY, BIOCHEMISTRY AND MoucuLAR BIOLOGY OF THE **SKIN** , VOLS. I AND II, Goldsmith (ed.), Oxford Press (1991), the full disclosures of which are ...

...cells, endothelial cells, activated lymphocytes, NK cells, LAK cells, astrocytes, smooth muscle cells, and other **epithelial** cell types. Agents in this category demonstrate at least 25% inhibition of TNF production/release...causes of a disease, or any other desired alteration of a biological system.
"Non-allergic **Skin** Inflammatory Condition" refers to an inflammatory condition of the sldn which is not solely mediated...

...other dermatologic disorders such as blistery dermatoses and collagen maladies; and extrinsic ageing of the **skin** , be it photoinduced or not. "Non-allergic Systemic Inflammatory Condition" refers to an inflammatory condition in all surface **epithelia** and include epidermal Langerhans cells. These cell types are also referred to as antigen presenting...

...responses against antigens that contact the body surface. When an immunogen is applied to the **skin** , some Langerhans cells migrate from the site into dermal lymphatics and are carried to the...

...the processed antigens to T cells. In macrophages, the level of class H expression is **increased** when the macrophage is activated. The murine class H system is highly analogous to the...

...NK cells, LAK cells, astrocytes, endothelial cells, smooth muscle cells, mast cells, keratinocytes and other **epithelial** cell types. This particular cytokine governs a wide variety of biological activities including: cytotoxic effects...

...1045 (1988)). More recent studies in man have shown that anti-TNF antibodies can significantly **improve** the clinical manifestations of this disease. Patients with active arthritis were treated with chimeric human...

...TNF (see, Elliott, et al.. Arthritis Rheum. 36:1681-1690 (1993)). After several weeks, significant **improvements** were seen in the Ritchie Articular Index, the swollen joint count, and in other clinical...with inactive MS (see, Hauser, et al., Neurology 40:1735-1739(1990)). In one study, **increased** TNF and interferon production by monocytes was observed just prior to exacerbation of the disease...

...rodent models of diabetes. Correspondingly, reduction of circulating TNF in obese rats caused a significant **increase** of the peripheral uptake of **glucose** . Others demonstrated that TNF directly interferes with the signaling mechanism of insulin through its receptor...

...HIV-positive patients alone and together with zidovudine (ZDV). The average HIV viral load was **increased** over baseline after treatment with PTX and ZDV, compared to higher levels in patients given...

...such as Crohn's disease and ulcerative colitis are of unknown origin yet show an **increased** production of TNF, IL-1, and IEL-6 (see, Braegger, et al., Ann. Allergy 72:135-141 (1994)). An **increased** density of TNF immunoreactive cells in tissue specimens was ...significantly to the pathogenesis of both Crohn's disease and ulcerative colitis by impairing the **epithelial** and endothelial membranes or by **increasing** inflammatory cell infiltration. As noted above, the largest organ in the body, the **skin** , also makes TNF. Since **skin** represents the border to a hostile environment, it needs an arsenal of biological weapons to...

...mechanisms, then disease ensues. Psoriasis is one example of a serious and socially debilitating inflammatory **skin** disease characterized by a breakdown in the control of proinflammatory cytokines. Other inflammatory **skin** disorders such as eczema, atopic dermatitis, acne, contact dermatoses, sunburn and even cancers manifest a similar loss of control of the mechanisms that regulate normal cytokine levels in the **skin** . Psoriasis is a relatively common **skin** disease that is thought to be genetically predisposed. This intractable condition is characterized by inflammation...

...First, elevated levels of immunoreactive TNF and its receptors have been demonstrated in lesional psoriatic **skin** by immunohistochemical staining. Further, **increased** TNF mRNA levels in biopsies and elevated TNF biological activities in suction blister exudates from lesional psoriatic **skin** have been recently reported. Various clinical studies have demonstrated **increased** circulating levels of TNF in patients with severe psoriasis, and a decline in circulating TNF...

...Eczema presents clinically as lesions of variable size not clearly defined from the surrounding normal **skin** and which are characterized by

itching, redness, and scaling. Atopic dermatitis (AD) is a chronically...

...have long been considered one of the hallmark features of the disease. Yet, when clinical **improvements** of AD were observed in patients treated with either cyclosporin A or IEFN-,y therapy children with AD indicated that circulating TNF levels were **increased** relative to those of normal children. Elevated IL-8 levels were also found in 41...

...it is logical and plausible that TNF plays the leading and central role in acute **skin** inflammation resulting from ACD. Irritant contact dermatitis (ICD) is more prevalent than allergic contact ...irritating agent. While exposure to low levels of irritants may have no effect on the **skin** , irritant dermatitis occurs when the intensity or duration of the exposure exceeds the repair capacity, of the **skin** or when the chemical elicits a nonspecific inflammatory response. The understanding of the pathogenesis of...

...the clinical symptoms of ICD (induced by 10% sodium lauryl sulfate), an 8-10 fold **increase** in TNF and IL-6 was observed many hours before the 2-3 fold **increase** in IL-I#, IL-2 and GM-CSF in the peripheral human **skin** lymph. Lastly, it has been shown that administration of anti-TNF antibody prevents the development...

...the development of irritant dermatitis.
Sunburn is a clinical manifestation of over-exposure to UV **light** . It has
been shown that there is an **increase** in the serum TNF level in man after UV treatment (see, Koch, et al., J...

...derives in part from a heretofore
unrecognized sequence of cellular events which leads to the **skin** inflammatory response. This sequence includes the phases of (1) accentuated transepidermal water loss caused by an insult, injury or other chemical or physical stimulus to the **skin** , (2) a consequent change in the ion gradients normally maintained in the **skin** , (3) the release of pre-formed cytokines which are stored in the secretory vesicles within...

...as well as new superior anti-inflammatory agents, methods and compositions. The perturbation of the **skin** 's barrier properties typically results from a disorganization of the lipids in the **stratum corneum** . Although lipids account for only a small percentage of the total **stratum corneum** weight, they are crucial for the provision of the **permeability barrier** by the **skin** . For example, ...has been found to result in a marked disruption in barrier function and thus, an **increase** in transepidermal water loss (TEWL). See Menon et al. (1985) J. Lipid Res. 26:418...

...chloride, and phosphorus ions. See Warner et al. (1988) J. Invest. Dermatol. 90:78 The **increased** ion flux caused by the accelerated water transit disrupts these homeostatic ion gradients in the...

...profiles for sodium, potassium, calcium, and chloride each possess a major inflection point at the **stratum corneum** -granulosuni junction. As discussed above, passive water loss can disrupt these **concentration gradients** and shift the inflection points. Without wishing to be bound by any particular theory, this **increased** water loss and the resulting passive ion flux and disruption of the ion gradients and cellular concentrations in the **skin** provide a signal for the **enhancement** of secretory granule formation and secretion. Interestingly, in most

secretory systems, **increases** in intracellular calcium concentration stimulate secretion. See Rubin (1970) Pharmacol. Rev. 22:389-428, Schoen ...

...keratinocytes. This is analogous to the situation in the parathyroid gland where decreased calcium concentrations **increased** parathyroid hormone secretion.
See Brown (1991) Physiol. Rev. 71:371
Specifically, preformed lipids; enzymes, including...

...and significantly, proteins, including preformed cytoldnes, such as TNF and IL-1, found in the **stratum corneum** are released by some secretory granules. For example, the presence of preformed TNF and IL-1 in the upper layers and in the intercellular domain of the epidermis/ **stratum corneurn** and in isolated enriched secretory granule (lamellar body) preparation has been confirmed by the inventors...

...immobilization in the lipid matrix, and the presence of naturally occurring antagonists in the granulosum- **stratum corneum** junction could be the protection mechanisms that serve to prevent inward flux of the preformed process and constitutively present in the stratum comeum. In fact, the **stratum corneum** could % function as the excretory or consolidating system for constitutively-produced cytokines. However, under a...

...the overall high local level of proinflammatory cytokines could initiate and/or propagate the local **skin** inflammatory and immune responses. Additionally, it has been found that like the granulocytes, epidermal keratinocytes, monocytic/macrophage cell types, and perhaps also other **epithelial** and endothelial tissues, initiate their production and/or release of proinflammatory cytokines using a common...

...cytosolic domains where either various promotional and regulatory mechanisms are activated to induce production or **enhance** the release of cytokines such as TNF-ci and IL These secondary messenger ions may...

...discussion herein has centered on techniques for regulating the rate of cytokine production in the **skin** , the same techniques will be applicable to modulating the formation and release of proinflammatory cytokines...
...et al. (1991) Adv. Drug DeL Rev. 7:313 There are several notable similarities between **skin** and mucosal membranes. For example, the buccal membrane is stratified in a like manner to the **skin** , with both tissues comprising polygonal cells at the basal membrane leading to squamous cells at...

...the non-keratinized tissues, such as the floor of the mouth and buccal mucosa, have **epithelia** , which, like the **skin** , act as effective rate-limiting steps to absorption. Therefore, the buccal **epithelium** can be regarded as having less completely differentiated keratinocytes as compared with the epidermis.
III...

...used to alleviate inflammation. Such assays also provide a means to identify compounds which can **enhance** the cytokine productions.
Thus, in one aspect, the present invention provides assays for screening putative **skin** immune modulating agents. The assays of the invention include a variety of formats which are identifying those agents capable of modulating the production of cytokines in keratinocytes or other **epithelial** tissues. Most generally, the assays of the invention will

comprise the steps of (i) inducing...
...II molecule in primary human keratinocytes, i.e., keratinocytes isolated from human tissues or human **skin** ; (ii) exposing a portion of the stimulated cells or tissues to putative **skin** immune modulating agent; and (iii) determining whether the putative agent is effective to modulate cytokine...

...and (v) the neutrophil chemotaxis assay for IL
(1) ELISA
ELISA techniques for evaluating the **skin** immune response are well-known in the art (see, e.g., Kenney, et al., J...

...TNF antibody, at a concentration of between about 0 15 1Lg1ml. The antibody solution is **allowed** to incubate in the wells for about 12-24 hours at 4'C in a...

...blocked with an inert protein, such as bovine serum albumin (BSA) in PBS, which is **allowed** to incubate in the wells for 1-3 hours. The blocking solution is discarded and...substrate (e.g. 1 mg/mL OPD/ 0.3% H202/0. 1 M citrate buffer) **permit** color development, with the intensity of color varying according to the amount of TNF specifically...

...bound antibody is then exposed to the supernatant taken from keratinocytes cultured with a putative **skin** anti-inflammatory substance. A second antibody, carrying a radioactive label such as "5I-modified tyrosine is added to the bound cytokine and **allowed** to incubate as described above. Typically the labelled antibody has a specific activity of about...

...concentration or the presence of various detergents or solubilizing agents (as is the case with **skin** homogenates and lamellar body preparations).
Generally, this procedure involves electrophoresing the cell supernatant samples on...information of a qualitative and quantitative nature. The strength of this procedure is that it **allows** visualization and localization of the distribution of a specific cytokine among various cell types or...used in the ELISAs.
(a) WEHI/L-929 Bioassays
The WEHI and L-929 bioassays **allow** for the determination of the concentration of biologically active cytokines. The most sensitive TNF bioassay...

...This reagent is metabolized to a colored end product only by viable cells and thus **allows** determination of the extent of)VEHI cell toxicity. Using a standard curve of serially diluted...
...of dead cells P
can be determined by the formula:
where OD,.P,,.., is the **optical** density of the solution in wells containing supernatant and OD,,.,, refers to the **optical** density of solution in control wells. The **optical** densities of the solutions is determined using standard methods. Alternatively, the TNF concentration may be...1 units determined for the supernatants of keratinocytes incubated with various concentrations of a putative **skin** immune modulation agent to determine the actual IL-1 concentration of the supernatants.
(c) B...keratinocytes incubated in an agent effective to modulate cytokine production will be associated with an **increase** or decrease in cell/HPF compared to control depending on whether the putative agent is effective to **enhance** or suppress cytokine production.
b. Measurement of Cytokine Gene Expression

In addition to examining the...

...is not always the case. For example, modifications of the protein after its synthesis may **increase** its stability without any corresponding changes in the mRNA. Conversely, **increases** in mRNA production may not translate into **increase** amounts of protein as (1) the mRNA is unstable; (2) translational interference or bottlenecks in processing prevent a corresponding **increase** in protein production; or (3) the protein produced is unstable. In addition, some drugs are...

...sequences of the cytokines of interest. The probes are labelled, e.g., with 31p, to **allow** detection of probe binding to the appropriate mRNA. However, nonradioactive labeling and detection procedures may...

...immunohistochemical analysis of level of protein expression, in situ hybridization is a qualitative procedure that **allows** the direct visualization of cellular mRNA levels in cultured cells or tissue sections (Remick, D fixed cells are incubated in **ethanol** , and the sample is hybridized with a DNA probe specific for the cytokine of interest...

...with hematoxylin, the distribution of the probe can be visualized at the level of the **light** microscope.
(3) RT-PCR
A very sensitive and powerful technique for assessing mRNA levels is...

...concentrations can be achieved by RT-PCR. Primers have been designed, acquired, and prepared that **allow** the study of several different mRNA species, including human TNF, IL-la, IL-10, ICAM...the cells and then incubated at 37'C overnight. Rocking the tubes during incubation will **improve** the digestion of the sample. If the proteinase K digestion is incomplete after overnight incubation...precipitate has formed. The DNA precipitate is removed and dipped in a solution of 70% **ethanol** and gently mixed. The DNA precipitate is removed from the **ethanol** and air dried. The precipitate is placed in distilled water and dissolved. Another commonly used...

...8.0, 4.2 M guanidine isothiocyanate, 0.5% Sarkosyl, and 0. 1 M 2-**mercaptoethanol**). Whole tissue is processed by homogenization in this buffer, while cultured cells are scraped into...

...centrifuged to recover the precipitated nucleic acid. The nucleic acid pellet is washed in 70% **ethanol** /30% diethyl pyrocarbonate (DEPQ-treated water, repelleted, dried, and solubilized in DEPC water. Kits are...are provided in PCT patent publication [WO 91/05210], incorporated herein by reference. The method **allows**0 the enzymatic degradation of any amplified DNA from previous reactions and reduces nonspecific amplification. The... potentially be a nonradioactive label, such as DIG-UTP. The probe is then isolated and **allowed** to hybridize with the mRNA in the sample of interest. Following hybridization, a ribonuclease is...

...to explore the transcriptional activity of a cytokine gene and answer questions regarding whether the **increase** in steady-state mRNA levels as assessed by Northern blot is due to an **increase** in the transcription of the gene or due to an **increase** in the stability of the mRNA (see, e.g., Zuckerman, et al., Immunology 73:460...cytokines and the use of such regulatory elements to identify agents effective to suppress or **enhance** the transcription of DNA sequences encoding proinflammatory cytokines. DNA sequences within or flanking a cytokine gene which is preferentially expressed in keratinocyte cells contain DNA sequence motifs which function to **enhance** or drive transcription of the cis-linked gene in

keratinocytes. These sequences are termed cytokine-specific transcriptional regulatory sequences. Such sequences are isolated and evaluated for their capacity to **enhance** or drive transcription of an operably linked reporter gene (e.g., chloramphenicol transferase, CAT) in ...

...not in other cell types which have also been transfected with minimal reporter constructs.
The **enhancer** region may be derived from the 5' flanking region of a cytokine gene, where the cytokine gene selected is normally expressed in primary human keratinocytes. The **enhancer** region will include at least that portion of the 5' flanking region which is bound...
...induced by cytokines which are produced as a result of stimulation of the keratinocyte.
The **enhancer** region can be obtained by isolation and purification from a
suitable genomic library, optionally using...

...pathway of the keratinocyte has been induced. Conveniently, a detectable signal will be visibly or **optically** detectable to facilitate screening of multiple samples simultaneously, for example using multiple-well microtiter plates...

...gene is preferred. Other suitable marker genes include fl-galactosidase and chloramphenicol acetyl-transferase.
The **enhancer** region and the marker gene will be incorporated into a suitable DNA construct by conventional...

...for easy construction, the DNA construct will be prepared from a bacterial plasmid where the **enhancer** , the marker gene, and usually a suitable promoter region, will be sequentially introduced in proper reading frame so that binding of a nuclear regulatory protein to the **enhancer** region will result in **increased** expression of the marker. The plasmid will usually include at least one antibiotic resistance geneor portions thereof including the **enhancer** ,
promoter, marker gene, and optionally antibiotic resistance gene, will be introduced by conventional transfection techniques into the starting keratinocytes. Suitable techniques include the use of reagents that **improve** chemical **permeability** , **electroporation** , and the like. After transfection, the keratinocytes will be screened based on antibiotic resistance to...

...described below.
Stimulation of MHC Class II Expression
Keratinocytes express and macrophages and B lymphocytes **increase** expression of surface MHC class II molecules when activated, for example by oy-interferon.
(1...NY, 1989.)

2 In vivo Models
Animal models that are widely viewed to reflect human **skin** disorders and
to have predictive ability in assessing the efficacy of various treatments for these...allergen challenge, concurrently with, and/or subsequent to the challenge. Several accepted animal models for **skin** disease are known, each useful to study different aspects of **skin** disease, for example, immediate-hypersensitivity reaction, delayed-type hypersensitivity reaction, non-immunologic contact urticaria, and the like.
See NON-STERoiDAL ANTi-INFLAmmAToRy DRUGS: PHARMACOLOGY OF THE **SKIN** @

Henby and Lowe (eds.), Basel, Karger (1989). With respect to **skin** irritation models in animals, inflammation and hyperplasia can be induced by topical application of a...

...Derm., 93:2 p. 322 (1989), which is incorporated herein by

10 reference. Further, compromised **skin** barrier can be modeled by topical acetone treatment. TPA causes epidermal inflammation and hyperplasia by...

...kinase C, a key regulator of epidermal growth and inflammation. The pathophysiologic alterations to the **skin** induced by TPA bear many similarities to the pathophysiologic alterations observed in psoriatic **skin** . **Skin** challenged with DNCB several days after sensitization has been observed to exhibit immunologic reactions similar to those observed in clinical cases of allergic contact dermatitis. Acetone treatment of the **skin** is known to cause physiologic alterations as a result of disruption of the **stratum corneum** barrier. Such alterations are commonly observed in **skin** diseases.
In addition to the use of normal mice where **skin** inflammation is induced
via topical application of a specific stimulating agent, relevant **skin** disease model can also be developed in immune-compromised mice such as athymic nude mice...

...143:1511-1522, 1993). In these immune-compromised, or immune-deficient mice, excised psoriatic lesional **skin** is transplanted to the back of the animal. Once healed completely, these xenografts can be...

...to model psoriasis in man. Similar approach can be applied to the development of other **skin** diseases, as well as infections.
The most common model for various **skin** cancers relies on the administration of a cancerous cell line or the implantation of cancerous ...

...onto the athymic mouse or SCID mouse. The compromised immune system of this animal will **allow** the development of cancers or tumors, often ... regulated by specific ligand such as cAMP, binding to the receptor. There are other calcium **permeable** channels that are not sensitive to the selective calcium channel blockers, which there are no...TNF production in stimulated RAW cells (62% inhibition at 10 ng/mL LPS), and TPAinduced **skin** swelling response in mice.
Preferred compounds useful in the present invention include the loop diuretics...diphenylcyclopropyl)-4,5-dihydro) [CAS 01-9]; CV-6402 (2,2'[(2-amino-ethyl)imino] **diethanolbis** (butylearbamate) 2HCL); EGIS-3966 (Cyclohexanone, 2-(phenylmethylene)-[3-[bis(I-methylethyl)amino] hydroxypropyl]oxime, (E ...decaenamide [CAS 48-6];
Carsatrin (4-[bis(4-fluorophenyl)methyl-ce-[(5H-purin ylthio)methyl]-**piperazineethanol**) [CAS 87-31; and BDF-9148 (4-[3'-l-(diphenylmethyl)-azetidine yl(oxy)-2'hydroxypropoxy...

...mouse peritoneal macrophages, PGE2 was found to effectively suppress lipopolysaccharide (LPS)-stimulated TNF production. The **increase** in intracellular cAMP levels produced upon interaction of PGE2 with ... adenylate cyclase (both G-protein activators and a-receptor agonists) also can be used to **increase** intracellular cAMP levels. Commonly used 0-adrenergic agonists (or,6-agonists) include albuterol, terbutaline, metaproterenol...

...production in THP-1, RAW and keratinocytes.
The net intracellular cAMP level can also be **increased** by inhibiting the
cAMP degradation. To this end, several inhibitors of phosphodiesterases (PDEs), the enzyme...

...Channel Blockers
Two of the three major structural classes of calcium channel blockers exist in **optically** active forms. Verapamil and diltiazem each have at least one **optical** center and accordingly can be separated into their respective enantiomers to determine the levels and...

...therefore exists as a single isomer. For other dihydropyridine agents which are not symmetrically substituted, **optical** isomers will exist due to the chirality associated with the C-4 position of the...that antiinflammatory properties are associated with both isomers of a racemic pair. Thus, a specific **optical** isomer of a calcium channel blocker can be selected to provide a desired therapeutic benefit conditions, such as infection and wound healing, elevated TNF production is beneficial to **enhance** the body's immune response to fight infections, and to facilitate removal of degenerated tissue...

...a calcium channel blocker. In preferred embodiments, for calcium channel blockers having one or more **optical** centers, a specific **optical** isomer of the calcium channel blocker is used. The specific **optical** isomer is preferably the isomer which is the less cardiovascularly active isomer. Alternatively, the specific **optical** isomer can be selected to provide optimal modulation of TNF production. In other preferred embodiments...

...channel blocker is a benzoacetonitrile, a dihydropyridine or a benzothiazepinone, more preferably as a specific **optical** isomer. Still further preferred are those embodiments in which a benzoacetonitrile, preferably verapamil, is present predominantly as its plus isomer. In one group of embodiments, the pathological condition is a **skin** inflammatory condition, preferably psoriasis, atopic dermatitis, UV-induced inflammation, contact dermatitis or inflammation induced by...

...administered to the mammal. As with the more general methods and for the treatment of **skin** inflammatory conditions, the preferred calcium channel blockers are benzoacetonitriles, dihydropyridines or benzothiazepinones, more preferably as a specific **optical** isomer. Still further preferred are those embodiments in which a benzoacetonitrile, preferably verapamil, is present...

...The preferred calcium channel blockers are benzoacetonitriles, dihydropyridines or benzothiazepinones, more preferably as a specific **optical** isomer. Still further preferred are those embodiments in which a benzoacetonitrile, preferably verapamil, is present predominantly as its plus isomer. In another aspect, the present invention provides methods of reducing **skin** adverse reactions associated with the application of transdermal devices to a selected area of the s1dn, comprising administering to the selected area of the **skin** an amount of a calcium channel blocker effective to reduce the adverse reaction in conjunction blocker has at least one **optical** center, a specific **optical** isomer is preferred, more preferably either that isomer which is the less cardiovascularly active isomer...

...the present invention provides a method of reducing s1dn sensitization and irritation associated with the **iontophoretic** delivery of a

therapeutic agent, comprising administering a therapeutically effective amount of a calcium channel blocker in conjunction with the **iontophoretic** delivery of the therapeutic agent. The administration of the calcium channel blocker to the **skin** can be made either prior to, contemporaneously with, or subsequent to the **iontophoretic** delivery of the therapeutic agent. In preferred embodiments, the calcium channel blocker is a benzoacetonitrile...

...application of a transdermal patch, above, the calcium channel blocker will preferably be a specific **optical** isomer (when the CCB has at least one **optical** center). More preferably that isomer is either the less cardiovascularly active isomer or the isomer...

...methods are provided for the treatment of ocular inflammation in a mammal and for reducing **skin** sensitization or irritation arising from the use of a cosmetic or **skin** care product. In each of these methods, an effective amount of a calcium channel blocker...spantide) or neurokinin-1 receptor antagonists (e.g., CP-96,345) can be administered to **ameliorate** the effect of this neuropeptide. Additionally, since acetylcholine is one of the most potent neurotransmitters...

...such as atropine, ipratropium
bromide, and the like can be effective in alleviating the immediate **skin**

inflammation/immune response.
Additionally, mast cell mediator release inhibitors, such as cromolyn sodium or sodium...

...useful in the methods described herein.
c. Antihistamines
Histamine can be released either from degranulating **skin** mast cells or peripheral nerve endings during the **skin** 's inflammatory/immune response. Histamine is known to produce the redness, wheal, and flare reactions in the **skin** . In addition, it has been suggested that histamine can work in synergy with TNF to...of histamine binding to the H-2 receptor that is of particular interest in the **skin** 's inflammatory/immune response. Thus, compounds known to be H-2 antagonists, such as cimetidine, and the like, either alone or in combination with **iontophoresis** , can be utilized in the methods described herein.
d. Immunosuppressants
The first evidence suggesting efficacy for the treatment of inflammatory **skin** disorders with immunosuppressants came from the systemic administration of cyclosporin A to psoriatic patients. Although...

...nephro- and hepatic toxicity, cyclosporin A has been employed in the treatment of many inflammatory **skin**0 disorders. Recently, it has been demonstrated that topical application of immunosuppressants, such as FK-506, was effective in inhibiting **skin** inflammatory reactions in an allergic contact dermatitis model. Other immunosuppressants, such as corticosteroids (see, e...

...ion (e.g., as the citrate, versenate, or other salt) delivered either passively or by **iontophoresis** (see, e.g., Diezel et al. (1989) J. Invest. Demat. 93:322-326); agents that...diethyl stilbestrol, and the like.
Additional pharmacological agents that can be delivered topically, transdermally, or **iontophoretically** , according to the methods described herein include other cytokines, peptides, oligosaccharide, proteins and oligonucleotides capable...to one group of embodiments, pharmacological agents capable
of modulating inflammation are applied to the **skin** , either

iontophoretically , **sonophoretically** , topically, or through other routes of drug administration, such as oral (PO), intraperitoneal (IP), intravenous...

...topical formulations will comprise a preparation for delivering a pharmacological agent directly to the affected **skin** comprising the pharmacological agent, typically in concentrations in the range from about 0. 00 1...modulating agents such as La". In preferred embodiments, for TNF inhibitors having one or more **optical** centers, a specific **optical** isomer of the inhibitor is used. In other preferred embodiments, the TNF inhibitor is a benzoacetonitrile, a dihydropyridine or a benzothiazepinone, more preferably as a specific **optical** isomer. Still further preferred are those embodiments in which a benzoacetonitrile, preferably verapamil, is present predominantly as its plus isomer. The specific **optical** isomer is preferably the isomer which is the less cardiovascularly active isomer. Alternatively, the specific **optical** isomer can be selected to provide optimal modulation of TNF production.
Additionally, other pharmacological agents

which have **optical** isomers are
also expected to show a stereoselectivity similar to that which is found with...of a topical formulation includes about 1 % (+)-verapamil by weight; about 35-40% alcohol, predominantly **ethanol** and isopropyl alcohol; about 30% propylene glycol; about 15% polyethylene glycol 400 (PEG 400); about 10% water; and small amounts, such as about 1 % or less, of each of **glycerin** , sodium laurel sulfate, stabilizers, preservatives, humectants, thickeners, and chemicals selected for the addition of color ...

...Pat. No. 4,940,587. This buccal adhesive formulation, when applied to the buccal mucosa, **allows** for controlled release of the pharmacological agent into the mouth and through the buccal mucosa...active on the eye surface or in the eye after passage through the cornea or **conjunctiva** . To **increase** bioavailability of drugs, to extend therapeutic efficacy, and to **improve** patient compliance, various dosage forms have been developed over the years. These include soluble inserts...

...patches have the added advantage of providing controlled delivery of a pharmacological agent to the **skin** or body. See TRANSDERMAL DRUG DELIVERY: DEVELOPMENTAL ISSUES AND RESEARCH INITIATIVES, Hadgraft and Guy (eds...

...incorporating the pharmacological agent in a proper medium, such as an elastomeric matrix material. Absorption **enhancers** can also be used to **increase** the flux of the compound across the **skin** . The rate of such flux can be controlled by either providing a rate-controlling membrane...

...backing material and an adhesive, such as an acrylate adhesive. The pharmacological agent and any **enhancer** , or combination of **enhancers** , are formulated into the adhesive casting solution and **allowed** to mix thoroughly. The solution is cast directly onto the backing material ... deliver the pharmacological agent. The layers of this patch comprise a backing, a polyurethane drug/ **enhancer** matrix, a membrane, an adhesive, and a release liner. The polyurethane matrix is prepared using...also find use in the methods described
herein. This patch comprises an impermeable or semi- **permeable** , heat sealable backing material, a heat sealable membrane, an acrylate based pressure sensitive **skin** adhesive, and a siliconized release liner. The backing is heat sealed to the membrane to form a reservoir which can then

be filled with a solution of the drug, **enhancers** , gelling agent, and other excipients. Such patches are described in U.S. Patent Nos. 5...

...incorporated herein by reference.
In one embodiment, a TNF inhibitor can be applied to the **skin** in conjunction with any device or delivery system which is attached to the **skin** through an adhesive, e.g., a transdermal patch or an ostomy device such as a...

...or more different drugs, or the benzoacetonitrile can be applied to the area of the **skin** upon which the patch is to be placed prior to attachment of the transdermal patch to the **skin** . Such a combination can be used to deliver systemic antiinflammatories or reduce the well-known problems of **skin** irritation caused by the attachment of a transdermal patch to the **skin** . The TNF inhibitors which act as antiinflammatories can also be applied after the patch is...

...a pharmacological agent and a sealing material overlaid on the outside, to the area of **skin** to be treated. Occlusion prevents loss of the drug from the **skin** , promotes **skin** hydration, and **increases skin** temperature. These actions have been shown to **enhance** the penetration of certain medications used in the treatment of psoriasis, leg ulcers, some dermatitis...polyethylene film (e.g., Vigilong, Bard Home Health Division, Berkeley Heights, NJ and Spenco 2nd **Skin** Dressingg, Spenco Medical Inc., Ward, TX); polyethylene (e.g., Glad Cling WrapO, Union Carbide Corp...

...to methods and apparatus for transdermal delivery
of therapeutic agents by means of an applied **electromotive force** to an
electrolyte-containing reservoir. The particular therapeutic agent being delivered may be charged or...

...ion, calcium ion, or any charged atom or molecule, the process is referred to as **iontophoresis** . When the therapeutic species delivered is uncharged, it may be considered delivered by means of...

...solvent, in which the uncharged species is dissolved, as a result of the application of **electromotive force** to the electrolyte reservoir. Of course during the process, some transport of charged species will take place as wen. In general, **iontophoresis** is an introduction, by means of electric current, of ions of soluble salts into the tissues of the body. More specifically, **iontophoresis** is a process and technique which involves the transfer of ionic (charged) species into a...

...That is, ions are transferred into the tissue, from an electrolyte reservoir, by application of **electromotive force** to the electrolyte reservoir.
If the electrotransport method is **iontophoresis** , generally the active electrode includes the therapeutic species as a charged ion, or a precursor for the charged ion, and the transport occurs through application of the **electromotive force** to the charged therapeutic species. If other electrotransport phenomenon are involved, the therapeutic species will be delivered in an uncharged form, transfer being motivated, however, by **electromotive force** . For example, the applied ...the non-therapeutic charged species induces movement of the therapeutic but non-charged species.
Through **iontophoresis** , either positively charged drugs (medication) or negatively charged drugs (medication) can be readily transported through the **skin** and into the patient. This is done by setting up an

appropriate potential between two electrode systems (anode and cathode) in electrical contact with the **skin** . If a positively charged drug is to be delivered through the **skin** , an appropriate **electromotive force** can be generated by orienting the positively charged drug species at a reservoir associated with the anode. Similarly, if the ion to be transferred across the **skin** is negatively charged, appropriate **electromotive force** can be generated by positioning the drug in a reservoir at the cathode. Of course...

...may be delivered from a single system during a selected operation. For general discussions of **iontophoresis** , see, e.g., Tyle (1989) J. Phann. Sci. 75:318; Burnette, **Iontophoresis** (Chapter 11) in TRANSDERMAL DRUG DELIVERY Hadgraft and Guy (eds.) Marcel Dekker, Inc.: New York...

...24, the full disclosures of which are incorporated herein by reference. A wide variety of **iontophoresis** devices are presently known. See, e.g., Phipps et al. U.S. Patent No. 4...

...of each which are incorporated herein by reference.
In typical, conventional, electrotransport devices, for example **iontophoresis** devices, two electrodes are generally used. Both electrodes are disposed so as to be in intimate electrical contact with some portion (typically **skin**) of the subject (human or animal) typically by means of two remote electrolyte-containing reservoirs, between which current passes as it moves between the **skin** and the electrodes. One electrode, generally referred to herein as the "active" electrode, is the...

...drug precursor or drug) is delivered or driven into the body by application of the **electromotive force** . The other electrode, typically referred to 1A 35 as an "indifferent" or "ground" electrode, serves...in these materials is not in their ability to generate an electric potential across the **skin** , but rather in certain nuances associated with their performance of this function. For example, platinum ...

...in pH can influence the ionization state of therapeutic agents and their resulting rate of **iontophoretic** transport. Silver-silver chloride electrodes, on the other hand, do not hydrolyze water. However, these...

...material. Such drug reservoirs, when electrically connected to the anode or the cathode of an **iontophoresis** device, provide a source of one or more ionic species for electrotransport. Generally, buffers will...

...ionic species, save the therapeutic agent itself, is minimized. In conjunction with the patient's **skin** in electrical communication with the electrodes, the circuit is completed by connection of the two...

...be the active electrode and the positive electrode (anode) will be the indifferent electrode. Chemical **enhancers** , vasodilators, and **electroporation** can also be utilized to alter the **iontophoretic** transport rate. For example, the coapplication of oleic acid to the **skin** causes a large decrease in the **skin** impedance or resistance which is inversely related to **permeability** or transport. See Potts et al. (1992) Solid State Ionics 53-56: ...ducts), the ions constituting the current can more uniformly permeate the lipid milieu of the **stratum corneum** at a lower current density. Thus, the epidermis, as well as the peripheral neurons surrounding...

...able to experience the electrical stimulation.

Substances which would perturb the normal structure of the **stratum corneum** could, in turn, disrupt the intercellular lipid organization, thus reducing its effectiveness as a dielectric barrier. These substances could include any lipid material which would partition into the **stratum corneum** lipids causing a direct effect or any material which would effect the proteins and cause an indirect perturbation of the lipid structure. Furthermore, solvents, such as **ethanol** , can remove lipids from the **stratum corneum** , thus destroying its lipid organization and decreasing its dielectric properties. Examples of **stratum corneum** lipid perturbants include, but are not limited to, alcohol **enhancers** , such as alkanols with one to sixteen carbons, benzyl alcohol, butylene glycol, diethylene glycol, glycofurol, glycerides, **glycerin** , **glycerol** , phenethyl alcohol, polypropylene glycol, polyvinyl alcohol, and phenol; amide **enhancers** , such as N-butyl-N-dodecylacetamide, crotamiton, N,N-dimethylformamide, N,N-dimethylacetamide, N-methyl...

...jojoba oil, petrolatum; mixes, such as primary esters of fractionated vegetable oil fatty acids with **glycerine** , or propylene glycol, and interesterified medium chain triglyceride oils; fatty acids and fatty acid esters...

...caprylic acid, cetyl ester, diethyl sebacate, dioctyl malate, elaidic acid ethyl caprylate, ethyl glycol palmitostearate, **glyceryl** beheate, **glucose** glutamate, isobutyl acetate, laureth-4, lauric acid, malic acid, methyl caprate, mineral oil, myristic acid...

...caprylic-, capric-, and lauric-triglycerides; macrocylics, such as butylated hydroxyanisole, cyclopentadecanolide, cyclodextrins; phospholipid and phosphate **enhancers** , such as dialkylphosphates, ditetradecyl phosphate, lecithin, 2-pyrrolidone derivatives, such as alkyl pyrrolidone carboxylate esters, pyroglutamic acid esters, N-methyl pyrrolidone, biodegradable soft penetration **enhancers** , such as dioxane derivatives and dioxolane derivatives; sulphoxide **enhancers** , such as dimethyl sulphoxide and decylmethyl sulphoxide; acid **enhancers** , such as alginic acid, sorbic acid, and succinic acid; cyclic amines; imidazolinones; imidazoles; ketones, such...nonoxynols, polysorbates, polyoxylene alcohols, polyoxylene fatty acid esters, sodium lauryl sulfate, and sorbitan monostearate.
In **electroporation** , which may have the same net effect as the use of chemical **enhancers** plus conventional **iontophoresis** , transient pores in the lipid structure of membranes, such as the stratum comeum, are created...

...been used to introduce DNA into various cells. See Chang et al. (1992) HANDBOOK OF **ELECTROPORATION** AND ELECTROFUSION Academic Press: New
York. Generally, **electroporation** involves the application of infrequent, short (about 1 millisecond), high voltage (5-300 volts) electric...

...the present invention, the
inflammation, irritation, and/or sensitization which frequently occurs with transdermal or **iontophoretic** delivery of drugs, and in other topical products such as cosmetics, can be **ameliorated** by pre-, co-, or post-administration of a TNF inhibitor. Such transdermaland **iontophoresis** -related inflammation is described in, e.g., Hogan, et al., J. Am. Acad. Dermatol., 22...

...includes the use of a TNF inhibitors or chemical anti-inflammatory agent

in conjunction with iontophoretic delivery of drugs to reduce the above-described sensitivity and irritation which accompanies **iontophoretic** drug delivery. Additionally, the TNF inhibitor can be used alone or in a combination of two or more. The agent or agents may be administered to the **skin** prophylactically, i.e., before the application of the **iontophoretic** current either topically or subcutaneously, or the agent or agents may be administered contemporaneously with the **iontophoretic** current, for example, by inclusion of the agent or agents with the reservoir of material to be delivered to the **skin** .

(8) **Sonophoresis**

Ultrasound also has been employed as a means of transdermal drug delivery, a technique known as **sonophoresis** or phonophoresis (see Type, et al., "Drug Delivery by Phonophoresis" Pharm. Res. 6:355-361 (1989) and Bommannan, et al., " **Sonophoresis** I: The Use of Ultrasound to **Enhance** Transdermal Drug Delivery" Phann. Res. 9:559-564 (1989), both of which are incorporated herein by reference). High frequency sound waves have been observed to disrupt the superficial **skin** layers (e.g., the **stratum corneum**); thereby **enhancing** the transport of drugs into the sldn. **Sonophoresis** has been reported to **enhance** drug delivery while avoiding the problems of **permeability** and long lag times before achieving therapeutically useful flux associated with other methods of transdermal drug delivery (see Bommannan (1989)). **Sonophoresis** at a frequency of 10-16 MHz has been shown to deliver materials into the **skin** in as few as 5 minutes (see Bommannan, et al., Phannaceutical Research, 9:8 1043-1047 (1992)). Thus, **sonophoresis** provides another method for the topical delivery of anti-inflammatory substances.

(9) Combinations

Combinations of the various techniques described herein, i.e., electrotransport, **sonophores**is , pharmacological intervention, and occlusion, can also be utilized. For example, pharmacological agents can be administered "actively" through the use of **iontophoresis** , or **sonophoresis** , optionally with **stratum corneum** lipid perturbants, or "passively", for example via the topical application of pharmacological agents, alone or with **stratum corneum** lipid perturbants. A further embodiment will combine **iontophoresis** with occlusion. Other embodiments will provide for the combination of occlusion and pharmacological agents. For...

...treatment may or may not be important depending on the disorder being treated. For example, **iontophoresis** and pharmacological intervention may be applied sequentially to the patient, with the **iontophoretic** therapy being administered before, during, after, or any combination thereof. Sequential administration involves treatment with...

...24 hours) and may involve continued treatment with the pharmacological agent on days that the **iontophoretic** therapy is not administered. The therapies may be administered to the patient at one time...

...agent may be applied to the affected area. Alternatively, a pharmacological agent may be delivered **iontophoretically** .
The optimal combination of therapies and their sequence will depend upon the type of disorder...

...the compound is that which provides either subjective relief of symptoms or an objectively identifiable **improvement** as noted by the clinician or other qualified observer. The dosing range varies with the...

...topical formulations will comprise a preparation for delivering a pharmacological agent directly to the affected **skin** comprising the pharmacological agent, typically in concentrations in the

range from about 0.001 % to...typically held in contact with the mucosal membrane and disintegrate and/or dissolve rapidly to **allow** immediate local and systemic absorption. For delivery to the buccal membranes, typically an oral formulation...

...Pat. No. 4,940,587. This buccal adhesive formulation, when applied to the buccal mucosa, **allows** for controlled release of the pharmacological agent into the mouth and through the buccal mucosa...active on the eye surface or in the eye after passage through the cornea or **conjunctiva** . To **increase** bioavailability of drugs, to extend therapeutic efficacy, and to **improve** patient compliance, various dosage forms have been developed over the years. These include soluble inserts...

...In one embodiment, a TNF inhibitor or an anti-inflammatory can be applied to the **skin** in conjunction with any device or delivery system which is attached to the **skin** through an adhesive, e.g., a transdermal patch or an ostomy device such as a...

...TNF inhibitor or the anti-inflammatory agent can be applied to the area of the **skin** upon which the patch is to be placed prior to attachment of the transdermal patch to the **skin** . Such a combination can be used to deliver systemic TNF inhibitors or antiinflammatories or reduce the well-known problems of **skin** irritation caused by the attachment of a transdermal patch to the **skin** . The TNF inhibitor or anti-inflammatory agent can also be applied after the patch is...usual patient treated with the invention may actually tolerate higher dosages of the inventive (+)-verapamil **better** than the conventional racernate because of the former's reduced effect on the cardiovascular system...

...10 to about 180 mg per day of (+)-verapamil is recommended. The dosage may be **increased** , usually in increments of about 10 to 100 mg, to a maximum of about 480...

...from about 2.8 to about 7.4 hours. After repetitive dosing,. the half-life **increased** to a range of from about 4.5 to about 12. 0 hours. When administered...a hydrated dressing and a sealing material overlaid on the outside, to the area of **skin** to be treated. As noted above for the use of occlusive methods with drugs, occlusion promotes **skin** hydration, and **increases** **skin** temperature.

3 Application of an Electric Field
Some embodiments of the present invention will employ...
...of an
electric field to modulate the lamellar body extrusion process. The application of an **electromotive** **force** has been discussed above in connection with **iontophoretic** delivery of therapeutic agents. The use of ion currents will find use in the treatment...

...to this embodiment the ion current can be produced by applying the anode of an **iontophoretic** delivery device capable of delivering an electric field with a net current typically, from about...

...and most preferably from about 0. 1 to about 0.5 mA, to the affected **skin** . Typically, the cathode reservoir comprises a conductive gel and the anode reservoir comprises an aqueous...

...described in U.S. Patent No. 5,221,254 to Phipps.
In some embodiment, the **enhancing** current will be applied by placing an electrode on the affected area and delivering an...

...most preferably, from about 20 to about 40 minutes. Moreover, since in the absence of **stratum corneum** lipid perturbants, the current density tends to concentrate on the shunt pathways, the release of...

...or cause mast cell degranulation and macrophage activation. The release of TNF-a from the **skin** mast cells and macrophages can further amplify the signal for keratinocyte activation induced by neuropeptides such as substance P.

Thus, the present invention contemplates the use of **enhancing** currents,

and the associated influx of ions into the **stratum corneum** -granulosum junction, optionally with **stratum corneum** lipid perturbants, to promote wound healing, to treat s1dn cancers, to **increase** local production of cytokines in order to fight infections, or to reduce inflammation.

4 Sonol2horesis...

...been employed as a means of transdermal drug delivery. This technique is also known as **sonophoresis** or phonophoresis. In the absence of therapeutic agents, these methods, (i.e., **sonophoresis**) through disrupting **stratum corneum** intercellular bilayers and the epidermal calcium gradients can modulate the epidermal immune responses associated with pro-inflammatory cytokine releases from lamellar bodies (see, Menon, et al., " **Sonophoresis** Disrupts Corneum(SC) Intercellular Bilayers and the Epidermal Calcium Gradient", Abstracts 100(4):497 (April...

...herein by reference.

Accordingly, the present invention provides methods for the treatment of inflammation using **sonophoresis** . Further, the present invention contemplates the use of **sonophoresis** and associated flux of ions into the **stratum corneum** -granulosum junction, optionally with **stratum corneum** lipid perturants, to promote wound healing, to treat **skin** cancers and to **increase** local production of cytokines in order to fight infection.

5 Combinations

Combinations of the various techniques described herein, i.e., electrotransport, **sonophoresis** , pharmacological intervention, and occlusion, can also be utilized. For example, pharmacological agents can be administered "actively" through the use of **iontophoresis** , or **sonophoresis** , optionally with **stratum corneum** lipid perturbants, or "passively", for example via the topical application of pharmacological agents, alone or with **stratum corneum** lipid perturbants. A further embodiment will combine **iontophoresis** with occlusion. Other embodiments will provide for the combination of occlusion and pharmacological agents. For...

...agents.

When combinations of the therapeutic methods described herein are used in the treatment of **skin** disorders, the particular sequence of treatment may or may not be important depending on the disorder being treated. For example, **iontophoresis** and pharmacological intervention may be applied sequentially to the patient, with the **iontophoretic** therapy being administered before, during, after, or any combination thereof. Sequential administration involves treatment with...

...24 hours) and may involve continued treatment with the pharmacological agent on days that the **iontophoretic** therapy is not administered. The therapies may be administered to the patient at one time...

...agent may be applied to the affected area. Alternatively, a

pharmacological agent may be delivered **iontophoretically** .
The optimal combination of therapies and their sequence will depend upon the type of **skin** disorder to be treated, the severity and course of that disorder, previous therapy, the patient...Field
It is well recognized that application of drug-delivering transdermal delivery systems to the **skin** can result in the development of an immediate or delayed-type contact sensitivity to the...

...drug delivery.
There are seven transdermal therapeutic systems presently on the market: scopolamine (motion sickness), **nitroglycerin** (angina), clonidine (hypertension), estradiol (hormone replacement), nicotine (smoking cessation), fentanyl (analgesic) and testosterone (hypogonadism). See...

...and especially chronic use of the
transdermal patches could be a result of the vehicle, **enhancer** , adhesive, drug, or any combinations of these components. Both irritant and allergic contact dermatitis have...

...method and agents mentioned in this application following the use of transdermal patches to further **improve** the safety profile and compliance of any given transdermal product.
Methods of pretreatment include applying one or more of the compounds described above to the **skin** in the form of a topical preparation such as an ointment, gel or cream about...of electrotransport to reduce irritation and sensitization resulting from such application.
B. The Treatment of **Skin** Diseases
One of the common clinical manifestations in **skin** diseases of diverse origins is compromised **skin** barrier function as evidenced by an **increase** in the transepidermal water loss (i.e., > 10% normal, as measured with an electric water...
...IL
The methods described herein will find use in the treatment of a variety of **skin** disorders, including those associated with differentiation and proliferation, for example, allergic dermatitis, psoriasis, eczematous or ...

...such as cutaneous T-cell lymphoma, blistery dermatoses and collagen maladies; and ageing of the **skin** , be it photoinduced or not. Examples of specific **skin** diseases amenable to treatment with the methods described herein include psoriasis, eczematous dermatitis and all TNF-mediated **skin** disorders. Psoriasis is a common, idiopathic chronic **skin** disease characterized by inflamed, scaling, **skin** lesions containing infiltrates of neutrophils, lymphocytes and monocytes.
According to the present invention, the term...Eczematous dermatitis is not a specific disease entity but a characteristic inflammatory response of the **skin** . Eczematous dermatitis is sufficiently serious to account for the highest incidence of **skin** disease. Approximately one-third of all patients in the United States seen by dermatologists have eczema.
This category of **skin** disease includes atopic dermatitis, lichen simplex chronicus, prurigo nodularis, stasis dermatitis, nummular eczematous dermatitis, dyshidrotic...
...In addition, this category includes eczematous dermatitis caused by allergic contact, photoallergic contact, and polymorphous **light** -induced eruption, as well as infections eczematoid dermatitis and eczematous dermatophytosis.
For acute diseases such...

...antagonists. In a preferred embodiment, IFN-a or IFN-a2 is administered in combination with **iontophoresis** to provide additional therapeutic

advantages. IFN-a serves to counteract the TNF that is secreted from the lamellar bodies and that can exacerbate the symptoms of **skin** disease. Additionally, the **iontophoresis** and/or the pharmacological intervention can be combined with occlusion. In another preferred embodiment, a diuretic such as furosemide or spironolactone is administered in a topical preparation to afflicted **skin** . In still another preferred embodiment a TNF-inhibitor such as verapamil or isradipine is administered topically to diseased **skin** . Also in a preferred embodiment anti-diarrheal agents such as loperamide or diphenoxylate is administered topically to diseased **skin** or use as prophylactic regimen. In additon, **skin** disease is frequently associated with perturbations of the **skin** 's barrier properties and hence, elevated levels of water loss. As described above, this water...

...to accelerate the lamellar body extrusion process and hence, the cellular growth rate associated with **skin** diseases. Without being limited to a particular mechanism, the therapeutical. goal in the treatment of certain **skin** diseases may involve stabilizing the lamellar body extrusion process and/or homeostatic intracellular ion concentrations...

...thus, maintaining local ion concentration and the rate of lamellar body extrusion, and keeping the **skin** inflammatory/immunological responses at quiescent state. This stabilization can be brought about through the use of suppressing ion current electrotransport therapy, **sonophoresis** , and/or pharmacological intervention.

C. The Treatment of **Skin** Cancers

The methods described herein can be applied to the treatment for a variety of dermal or epidermal **skin** cancers, that are benign or malignant, of viral origin, bacterial, or other origin, including but...

...squamous cell carcinoma, mycosis fungoides lymphoma, and Kaposi's sarcoma. Primary malignant melanoma of the **skin** is the leading cause of death from all diseases arising in the **skin** . There has been a disturbing **increase** in the incidence of primary melanoma of the **skin** . The rate has doubled in the past 10 years, possible due to **increased** "weekend" exposure to sunlight. Primary cutaneous malignant melanoma, moreover, does not respond or responds only...

...primary stages before deep invasion occurs.

Basal cell carcinoma accounts for over 75 % of all **skin** cancers. These carcinomas arise from the epidermis, cytologically resemble the normal basal cells, and show...

...from a premalignant lesion, a bum sear, a chronic inflammatory condition, or from apparently normal **skin** .

Mycosis fungoides lymphonia is the most common lymphoma of the **skin** and begins with cutaneous lesions, usually with no evidence of visceral infiltration for several years...

...be clinically confused with eczema, contact dermatitis, or psoriasis. Kaposi's sarcoma is a frequent **skin** neoplasm that occurs in humans infected with HIV It is a complex neoplasm that includes...

...the natural defense mechanism to treat abnormal cell growth (various cancers and tumors) of the **skin** . In addition, the lamellar body extrusion process may also **increase** the rate of release of preformed proinflanimatory cytokines, such as EL-1 and TNF, and...

...accomplished by modulating the ion flux, ion gradients, or cellular concentrations of ions in the **skin** , for example, by using electrotransport, or **sonophoresis** , or with pharmacological intervention

or with combination of pharmacological agents and **iontophoresis** , or with **sonophoresis** . In addition, several different compounds are said to
WO 95/27510 PCTfUS95/04677
79
D...

...to tissue infarction followed by secondary inf
of the causes of chronic ulcers of the **skin** includes circulatory disturbances, such as varicose veins and obliterative arterial disease, ...and subsequently, promoting wound repair. Another therapeutic regimen which is presently under clinical development is **skin** or epidermal allographs. These treatment regimens involve major surgical procedures and significant medical costs and...

...by either pharmacological means (e.g. digoxin) or electrical means will initiate antigen-independent local **skin** inflammatory responses and the release of proinflammatory cytokines from lamellar granules. The release of TNF...
...1 stimulates both partial and full thickness wound repair in pigs via inducing the re- **epithelization** process.
The release of these proinflammatory cytokines can be accomplished by using **sonophoresis** , **iontophoresis** with an **enhancing** current, either alone or in combination with other pharmacologically active agents (e.g., growth factors...of a solution,
suspension, ointment, in a pack, by intracameral, subconjunctival or retrobulbar injection, or **iontophoreti**cally . Typically, a solution is preferred, the solution having a viscosity between about 15-25 centipoise ...

...to those of skill in the art.
F. Treatment of Inflammation Associated With Cosmetics or **Skin** Care Products
The compounds of the invention can also be used to alleviate **skin** sensitization, irritation or inflammation associated with cosmetics or **skin** care products. Preferably the compounds are TNF-inhibitors or ion modulating agents such as La...

...inhibitors or antiinflammatory agents described herein can be used before, during or in response to **skin** sensitization, irritation or inflammation associated with cosmetics or **skin** care products.
Typical **skin** care products and cosmetics which may cause adverse **skin** reactions such as sensitization, irritation or inflammation include depilatories such as described in U.S...be effective in reducing TNF activities in vitro and were both effective in vivo in **improving** cachexia conditions in cancer and AIDS patients respectively. Therefore, TNF has been found to be...

...or modified to yield essentially similar results.
V. EXAMPLES
A. Animal Models
Example: Induction of **Skin** Inflammation and Hyp=lasfic Responses by TWical TPA Treatment
The effects of the application of TPA to the **skin** have been well characterized in the literature. This activator of protein kinase C results in...

...of TPA treatment to stimulate the expression of cytokine messenger RNA (mRNA) in hairless mouse **skin** was examined in a preliminary time course ...of this experiment were analyzed by standard RT-PCR techniques on mRNA extracted from whole **skin** . The expression of

0-actin, a housekeeping gene whose expression is relatively constant under treatment...

...was not detectable at any of the time points examined. Lastly, TPA treatment of the **skin** caused the induction of ICAM-1 protein expression. Frozen **skin** sections were immunostained with a specific anti-ICAM-1 antibody and showed little or no...

...the experiments can be performed, the TPA treatment protocol was pursued as a model of **skin** inflammation. Detailed time course studies were therefore performed to determine the time point after TPA...

...In addition to assessing the cytokine mRNA levels, the time course of the TPA-induced **increase** in **skin** thickness was also evaluated. This measurement was made with a micrometer using **skin** excised from euthanized mice. While a minimal change in **skin** thickness was evident at the 2 hour and 4 hour time points, a dramatic **increase** was observed 6 hours after TPA treatment. Further **increases** were typically seen 8 hours with this response being maintained through the 24 hour time cytokine protein production in response to application of TPA to hairless mouse **skin** was also evaluated. **Skin** samples excised from euthanized mice were flash frozen and stored at -70'C until analysis...

...ELISAs for murine TNF and IL As compared to vehicle-treated tissue, the TPA treated **skin** showed little change in TNF content through the 6 hour time point. At 8 hours, however, a large **increase** in the TNF concentration of the homogenized **skin** was observed (approximately 300 pg/mL TNF) with lower levels of TNF being observed at...

...approximately 175 pg/ml). The profile of expression of IL-10 protein in TPA-treated **skin** was slightly different. **Increases** in IL-10 concentrations were gradually evident at 4 hours and 6 hours post-TPA, with the greatest **increase** being evident at the 8 hour time point (approximately 425 pg/ml). This IL-10...

...each being treated as 1) control, 2) vehicle, 3) verapamil. alone (4 % w/v in **ethanol**), 4) TPA alone, and 5) TPA + verapamil. Verapamil was applied to the **skin** the afternoon prior to the experiment,, 2-3 hours before the application of TPA, and...

...euthanized at a 24 hour time point, and the thickness of the treated areas of **skin** was measured using a micrometer.
The results of the RT-PCR analysis demonstrate that the low levels of TNF mRNA expression in control **skin** were unchanged or slightly reduced by treatment of the **skin** with vehicle (2.5 % **DMSO** in **ethanol**) or verapamil alone. Application of
TPA to the **skin** caused a substantial **increase** (104%
- 163%) of the TNF mRNA levels. Treatment of the TPA sites with verapamil resulted in a significant reduction ($p < 0.01$, paired Student's t test) in **skin** TNF mRNA levels as compared to TPA alone. In addition, the RNA samples from onein KC mRNA levels. Twenty-four hours after TPA application to the **skin** , the TPA sites looked markedly swollen and edematous as compared to the control sites, while...

...measurements, which demonstrated that verapamil afforded a substantial reduction in the extent of TPA-induced **increase** in **skin** thickness. Compared to **skin** treated with TPA alone, combined treatment with TPA + verapamil resulted complete suppression of **skin** swelling response. A slightly different protocol was used in an effort to determine whether the drug loperamide would also exert an anti-inflammatory effect on TPA-treated hairless mouse **skin** . Loperamide (7.5% solution in 70%

propylene glycol/30% **ethanol**) was applied the afternoon before, 2 hours before, and just after application of TPA. At the 8 hours time point, the mice were euthanized, the treated areas of **skin** were excised, and the thickness of the **skin** was measured using a micrometer. The results demonstrated that the thickness of **skin** treated with loperamide alone was unchanged as compared to vehicle-treated **skin** . A substantial **increase** in **skin** swelling was observed upon TPA treatment, with a thickness of 0.56 mm being measured...

...compared to 0.36 mm for vehicle-treated sites. Application of loperamide to TPA-treated **skin** sites was found to completely inhibit the TPA-induced **increase** in **skin** thickness at the 8 hour time point, with a 0.39 mm thickness being measured for the TPA + loperamide group (not statistically different from the vehicle-treated **skin**). The anti-inflammatory effects of loperamide were confirmed in a second experiment. In this study, **skin** thickness was observed to **increase** from 0.39 mm for vehicle-treated **skin** to 0.89 mm for the TPAtreated sites. Application of loperamide inhibited the TPA-induced...

...this phenomenon. The sequence of events following initial application of a contact allergen to the **skin** (sensitization phase) is thought to involve presentation of the allergen in association with NMC class...

...where they stimulate antigen-specific T cell proliferation. When the allergen is reapplied to the **skin** several days later (challenge phase), an allergic reaction occurs that takes 24-48 hours to...involved the application of DNCB (in an acetone:olive oil 4:1 vehicle) to the **skin** on the posterior portion of the back of hairless mice. Five days later, DNCB was...

...initial experiment was performed in which verapamil (4 % w/v in 70 % propylene glycol: 30 % **ethanol**) was applied to the dorsal and ventral surfaces of the right ear 2 hours before...

...with DNCB, and, five days later, amiloride (2% w/v in 70% propylene glycol: 30% **ethanol**) was applied to the right ear and vehicle to the left ear 30 minutes and...

...of cytokine protein expression in the DNCB contact hypersensitivity model. In these experiments, a significant **increase** in ear thickness was observed 18 hours post-DNCB challenge, peak swelling occurred at 30
Skin Barrier Model:
Acetone Treatment and Detection of TNF mRNA levels by RT-PCR
Hairless mice...

...Simonsen
Laboratories (Gilroy, CA). The animals were housed under standard conditions with a 12 hour **light** /dark cycle and free access to food and water. The mice were anesthetized with an...

...the mouse was euthanized by carbon dioxide asphyxiation. The control and acetone-treated areas of **skin** were removed and frozen on dry ice. RNA was extracted from the **skin** , and TNF mRNA levels were analyzed by standard RT-PCR procedures as described above. The...

...results of the acetone treatment demonstrated that, at a 2 hour time point, saline-treated **skin** showed little or no TNF mRNA expression, while a marked induction of TNF mRNA was evident in the acetone-treated **skin** .
B. Determination of Ion Concentrations
The quantities of ions at each stratum of the **skin** (one micron,

horizontal cryo-sections) can be analyzed either with elemental analysis, via atomic absorption...

...of the proinflammatory cytokines , e. g. @ IL- 1 and TNF , at each stratum of the **skin** can be measured semi-quantitatively by immunohistochemical staining of the whole **skin** tissue or quantitatively using standard, commercially available ELISA kits (Genzyme Cambridge, MA. or R&D...

...mRNA corresponding to TNF using PCR and Northern blot techniques as described above. Generally, the **skin** is challenged to produce an inflammatory response and the levels of cytokines are measured. Three...

...of Lamellar Bodies (LB) and
The Detection of TNF and IL-lot in LBs and **Skin**
LB Isolation
One hundred fifty to two hundred neonatal ICR Swiss albino mice (born within...the precursor form of IL-la.
Immunohistochemical Localization of TNF in
Phorbol Ester-Stimulated Murine **Skin**
Hairless mouse **skin** was treated topically with TPA in **DMSO / ethanol** for
various lengths of time, or with **DMSO / ethanol** alone, and was subsequently biopsied and either frozen immediately in a polyvinyl alcohol based embedding...

...for 2 hours, followed by immersion in a cryoprotectant buffer (e.g., 7% sucrose, 10% **glycerol** in cacodylate buffer) before freezing in OCT. The **skin** samples were sectioned in a cryostat and were used for immunohistochemical localization of TNIF. A...

...Vector laboratories) and either A-EC (3-amino ethylcarbazole), DAB (3,3'-diaminobenzidine), or silver- **enhanced** Auroprobe streptavidin (Amersham) end products. Slides were visualized and photographed in a Nikon Optiphot **light** microscope. The results demonstrated striking differential labeling patterns suggesting:
(1) dense outer epidermal localization consistent...

...similar loss of density in the SC/SG region following TPA treatment with a concomitant **increase** deeper into the nucleated cell layers suggests a similar mode of action for these two cytokines following TPA treatment. Like TNF, IL-la demonstrated also an **increased** density in the outer epidermis after 8 hours of TPA treatment. TPA-treated or untreated...

...of Transoidermal Water Loss
To determine the ability of compounds or methods described herein to **increase** or decrease the rate of barrier recovery during transepidermal water loss (TEWL), and thereby measure the "quality" of the **skin** with respect to the passage of water, and standard procedures used to disrupt the **stratum corneum** layer of the **skin** (e.g., the application of acetone to the **skin**). The time required for restoration of normal barrier function was also determined. Treatment of **skin** with sodium laurel sulfate (SLS) under occlusion (1.5 mg/cm' in saline) for a period of 7 to 20 hours was found to produce 20- to 200-fold **increases** in TEVYFL. Overnight exposure to SLS was found to be preferred. Barrier recovery was determined...

...10 %
fetal bovine serum, 2 mM L-glutamine, 25 mM HEPES, and 50 ItM 2-**mercaptoethanol** . Cultures were maintained by the addition of fresh

growth medium to a T-75 or...

...cell viability were assessed by the MTT assay. Drugs were prepared in a vehicle which **allows** for their complete dissolution, such as **DMSO** (for amiloride, for example) or **ethanol** (for verapamil, for example). Water-soluble drugs were dissolved in aqueous solutions such as RPMI or deionized H20. The final concentration of **DMSO** in the incubation medium was at or below 0. 0 1 % and that of **ethanol** was at or below 0. 1 The ...per well on the day prior to experimentation. Drugs were prepared in a vehicle which **allowed** for their complete dissolution, such as **DMSO** (for amiloride, for example) or **ethanol** (for verapamil, for example). Water-soluble drugs were dissolved in aqueous solutions such as RPMI or deionized H20. The final concentration of **DMSO** in the incubation medium was at or below 0. 03 % and that of **ethanol** was at or below 0. 1 %. Drugs were co-administered with the stimulant, LPS. After...at 4'C and for 1 hour at 37'C, to enable removal of the **stratum corneum** , separation of epidermal from dermal tissue and isolation of basal/suprabasal cells. The keratinocytes were...

...drug in our in vitro screens. TPA stock solutions were prepared in tissue culture grade **dimethyl sulfoxide** (**DMSO**) at 1 mg/mL and stored in aliquots at -20'C. Drugs were prepared in a vehicle which **allows** for their complete dissolution, such as **DMSO** (e.g., amiloride) or **ethanol** (e.g., verapamil). Water-soluble drugs were dissolved in aqueous solutions such as RPMI or deionized H20. The final concentration of **DMSO** in the incubation medium was at or below 0.03% and that of **ethanol** was at or below 0.2%. Drugs were screened for their ability to alter stimulated...of sample). Treatment of cells with 10 nM or 50 nM TPA produced a maximal **increase** in TNF mRNA levels by 50% at the 2-hour time point which declined over...

...on TPA-stimulated production of TNF in keratinocytes. These drugs were of particular interest in **light** of their effects on LPS stimulated cytokine production in RAW and THP-1 cells. Hexamethylamiloride...

...ng/mL), retinoic. acid (RA; 1 14M), or LPS (100 jAg/mL) resulted in an **enhancement** of the levels of the cell-associated form for the incubation times chosen (24-, 36...

...average amount of cell-associated IL-la detected was - 1800 pg/mL (a 6-fold **increase**). The maximum effect of 1 /AM RA was a - Mold **increase** at the 48 hr time point and that for 100 jAg/mL LPS was - 4...Dianosis
The methods described herein will find use in the treatment of a variety of **skin** disorders having an inflammatory and/or immunological component. In order to employ the optimal therapeutic method, the **skin** disorder should first be properly diagnosed. In addition, subsequent to the application of the methods described herein to the affected **skin** , an evaluation of the affected **skin** must be made in order to determine the efficacy of the treatment. Generally, the evaluation and diagnosis of a **skin** disorder is performed by compiling the patient's description of their symptoms, i.e., the...

...their own observations in an effort to recognize a pattern which identifies the disorder.
Many **skin** disorders can be diagnosed by physical examination alone. The patient will typically undress and undergo...

...which identify especially serious conditions such as cancer or AIDS. The signs and symptoms for **skin** disorders are well-known and have been complied in such references as TBE MERCK MANUAL area is less than or

equal to 20% of normal or healthy **skin** , i.e. , those areas not affected by the condition. More definitive assessments of both the...

...More specifically, one embodiment of this invention is drawn to the treatment of psoriasis with **iontophoresis** , optionally in combination with pharmacological intervention and/or occlusion. Psoriasis is characterized by symmetrical erythematous, scaling plaques on the **skin** surface. The involved (lesional) **skin** is thickened and may be mildly pruritic. It is upon these physical parameters and symptoms...

...area and severity index) which takes into account the total body surface area of lesional **skin** , as well as the degree of erythema, scaling, and thickness to evaluate the efficacy of...

...for methods for treating WO 95/27510 PCT/US95/04677
100
G. The Treatment of **Skin** Inflammatory Diseases with a Solution of Ions using **Iontophoresis**
This therapeutic regimen is applicable to **skin** conditions or diseases having an inflammatory and/or immunoallergic component. In addition, these methods may...

...reservoir (typically, 2-10 milliliters (ml)) having a semipermeable membrane for placement next to the **skin** .
The donor compartment is filled with an ion solution. The return compartment is filled with...The therapy is repeated as necessary. After one day of therapy, the TEWL of the **skin** over the affected area is
measured using a standard electrolytic device. If the TEVVL is...

...not affected by the condition, then the ionic solution is combined with a combination of **glycerin** /oleyl alcohol, or other **stratum corneum** perturbants, so as to not change the final ion concentration of the solution. Preferred combinations of **glycerin** and oleyl alcohol in percent by weight will include 0 15 percent **gly**cerin and 0 10 percent oleyl alcohol. More preferably the combinations will include 0 2 percent **glycerin** and 0. 1-5 percent oleyl alcohol.
The solution containing the ions and the **stratum corneum** perturbant is
then applied topically to the affected area 5 to 10 minutes prior to administration of the **iontophoretic** device. The **iontophoretic** treatment described above is then repeated. This combination of topical and **iontophoretic** treatments can be repeated as necessary.
*4P H. The Reduction of Irritation in Conjunction with...gel was prepared containing, in percent by weight,
loperamide (2.0%), Carbopol. 940' (1.5%), **triethanolamine** (1.5%) with water maldng up the remainder.
K. TMical **Skin** Delivery of Verapamil Formulations
Various verapamil formulations (at 80% verapamil saturation) were prepared (see Table) and topical **skin** delivery (i.e., verapamil delivered to the epidermis and dermis) from these formulations to excised human **skin** was accessed using flowthrough diffusion apparatus. Verapamil formulation (50 jil/cm') was applied topically three...

...sIdn was removed from the diffusion cell, excess formulation was wiped off the surface, the **stratum corneum** was stripped off the **skin** by tape, and the remaining epidermis and dermis was weighed. Total verapamil delivered to the epidermis and dermis was extracted by **ethanol** and was quantitated by high-performance liquid chromatography. The concentration of verapamil in the **skin** was calculated based on the amount of

verapamil extracted and the total weight of the...

...the following Table, the gel formulation delivers the highest quantity of verapamil to the human **skin** .
Summary of **Skin** Delivery Profile from
Various Verapamil Formulations
VRP
(Conc.) VRP/
No. Formulation in 80% **Skin**
Sat'd Mean
Solution mg/mL FM
1 GP/water (30/70) 59.7 856...

...5 ETOH/water/oleic acid 307.6 2081.73
(50/49.75/0.25)
6 **Glycerin** /water/oleic acid 15.4 @1 . @74
1(50/49.75/0.25)
Gel
7...

...47
carbopol/water
(20/10/20/0.4/1/48.6)
Ointment
8 White petrolatum/ **light** mineral oil 100.0 - 55.26
(55/45)
L. Prevention or Reduction of Transdermal Drug...

...administered in conjunction with a transdermal patch such as a clonidine transdermal patch (Catapres-TTSI&). **Skin** is pretreated with the anti-inflammatory formulation at a 50-200141 per cm' dose for...
...be applied about two hours prior to the application of the patch at the same **skin** site as well as following the removal of the patch. Local adverse **skin** reactions, i.e., relative irritancy potential (21-day cumulative irritancy assay) and allergic contact dermatitis...

...posttreatment regimen are tested to achieve the best result with respect to minimize these adverse **skin** reactions.
M. The Use of Specific Isomers of Calcium Channel Blockers to Modulate TNF-Mediated...

...verapamil is much more effective than thalidomide or pentoxifylline.

2 VeWamil for the Prevention of **Skin** Inflammation in Mice
This example illustrates the ability of (+/-)-verapamil to prevent **skin** inflammation induced by 2% sodium lauryl ...chamber. Following the 24 hour exposure, the Hilltop chambers were removed and, after 18 hours, **skin** thickness readings were taken. The results indicate that within minutes of removing the 2% SLS...

...the flanks exposed to SLS and verapamil, no effects of SLS irritation were observed. The **skin** thickness measurements for the treated flanks as well as for untreated **skin** are provided in the table below.
Table
Verapamil Prevention of **Skin** Inflammation
Treatment Visual Observation **Skin** Thickness
(mm, n = 4)
2% SLS Wound 1.23 0.11
SLS/Verapamil Normal 0.65 0.09
Untreated **Skin** Normal 0.59 + 0.08

As the results in the table indicate, edema developed in...

...in the SLS/verapamil-treated sites. Thus, verapamil was effective in preventing the development of **skin** inflammatory responses in mice.

3 Use of V"a amil for the Treatment of **Skin** Inflammation in Humans
This example illustrates the use of (+/-)-verapamil for the treatment of **skin** inflammation models in humans.
Human **skin** inflammation was elicited by either 2% sodium laurel sulfate in normal volunteers (irritant contact dermatitis...

...two respective sites. At the end of the two-day topical treatment, the degree of **skin** inflammation (i.e., erythema, edema and blister formation was assessed by a trained dermatologist. **Skin** biopsies were taken from the placebo and the active sites and analyzed for **skin** thickness and TNF levels using immunohistochemical techniques. The results of the biopsy analysis indicated that there is an **increase** in the TNF protein level and **skin** thickness of biopsies derived from the placebo sites in 50% of the patients and that...

...2 out of 3 for each test) treated with verapamil showed less TNF in the **skin** biopsies (see Figure 5). Further, **skin** thickness was less in 4 out of 6 patients on verapamil-treated sites than that...

...placebo sites (see Figure 6). Thus, verapamil was found to suppress irritant and allergen-induced **increases** in TNF production and **skin** thickness in humans.
Additionally, dermatitis was also found to resolve faster on verapamil treated sites...

...pro-inflammatory cytokine TNF production, mitigates hyperproliferative responses and demonstrates anti-inflammatory properties in a **skin** inflammation model in man.

4 Use of (+)-vg@rapamil for the treatment of atopic dermatitis...patient is treated with topical (+)-verapamil in a topical vehicle applied directly to the psoriatic **skin** areas three to four times a day until a therapeutic benefit is achieved. Thereafter, the...

...verapamil in a cream vehicle of concentration 1 % (weight/volume) applied directly to the afflicted **skin** areas twice a day until a therapeutic benefit is achieved. Thereafter, the cream is applied...

...weight/volume) (+)-verapamil in a cream vehicle. The preparation is applied directly to the afflicted **skin** areas twice a day. Applications are continued until a therapeutic benefit is achieved. Thereafter, the...
The (+)-verapamil is started at 20 mg twice a day. If tolerated, the dosage is **increased** in increments of 20 mg daily until a therapeutic benefit is achieved.
If needed, (+)-verapamil...

...of the addition of (+)-verapamil to the patch, the patient does not experience unacceptable local **skin** irritation at the site of application of the patch.

10 The use of (+)-veWamil to...full scope of equivalents.
WHAT IS CLALWED IS:
1 A method of screening for a **skin** immune or inflammation modulating agent, comprising:

i. stimulating production of at least one cytokine or...

...H
molecule in keratinocyte cells;
ii. exposing a portion of said cells to a putative **skin** inflammation modulating agent; and
iii. determining whether said putative agent is effective to modulate cytoldne...claim 1, wherein said determining further comprises identifying whether said putative agent is effective to **increase** said production of cytoldne or MHC Class II molecule in said exposed keratinocyte cells relative to said unexposed keratinocyte cells.

14 A method of screening for a **skin** immune or inflammation modulating agent, comprising:
i. inducing production of at least one cytokine or...

...II
molecule in keratinocyte cells;
ii. exposing a portion of said cells to a putative **skin** inflammation modulating agent; and
iii. determining whether said putative agent is effective to modulate the
...

...claim 14, wherein said determining further comprises identifying whether said putative agent is effective to **increase** said production of cytokine or MHC Class II molecule in said exposed keratinocyte cells relative to said unexposed keratinocyte cells.

20 A method of screening for a **skin** immune modulating agent, comprising:
L exposing a portion of keratinocyte cells which have been transformed...

...I@MC Class H molecule expressing gene linked to a reporter gene to a putative **skin** immune modulating agent;
ii. determining whether said putative agent is effective to modulate the transcription...

...genes.

22 The method of claim 20, wherein said measuring comprises measuring the amount of **light** produced by said exposed cells.
23 The method of claim 20, wherein said cytokine is...

...claim 20, wherein said determining further comprises identifying whether said putative agent is effective to **increase** production of ...keratinocyte cells.

26 A method of modulating an inflammatory response in sldn, comprising exposing said **skin** to an electric field which is effective to modulate production of cytokines or NMC Class II molecules in said **skin** , wherein said inflammatory response is modulated.

27 A method of administering a **skin** inflammation-inducing drug to sldn, comprising administering said drug to said sldn in conjunction with an **iontophoretic** current, wherein said **iontophoretic** current is effective to modulate the production of cytoldnes in said sldn.

28 A method...

...method in accordance with claim 28 wherein said calcium channel blocker has at least one **optical** center and is present predominantly as a specific **optical** isomer.

31 A method in accordance with claim 30 wherein said **optical** isomer is the less cardiovascularly active isomer of said calcium channel blocker.

32 A method in accordance with claim 30 wherein said **optical** isomer provides the optimal modulation of TNF production in said mammal.

33 A method in...

...comprises diltiazem.

36 A method in accordance with claim 28 wherein said condition is a **skin**

inflammatory condition.

37 A method in accordance with claim 36 wherein said **skin** inflammatory condition is a member selected from the group consisting of psoriasis, UV-induced inflammation and irritant contact dermatitis.

38 A method in accordance with claim 36 wherein said **skin** inflammatory condition is psoriasis.

39 A method in accordance with claim 36 wherein said **skin** inflammatory condition is irritant contact dermatitis.

40 A method in accordance with claim 36 wherein said **skin** inflammatory condition is UV-induced inflammation.

41 A method in accordance with claim 36 wherein said **skin** inflammatory condition is induced by Retin-A.

42 A method in accordance with claim 28 wherein said condition is a **skin**

adverse reaction associated with the application of a transdermal patch to a selected area of the **skin** , comprising administering to said selected area of the **skin** an amount of a calcium channel blocker effective to reduce said adverse reaction in conjunction...

...in accordance with claim 28 wherein said condition is sIdn sensitization and irritation associated with **iontophoretic** delivery of a therapeutic agent, comprising administering therapeutically effective amount of a calcium channel blocker in conjunction with said **iontophoretic** delivery of said therapeutic agent.

50 A method in accordance with claim 49 wherein said administration is made prior to said **iontophoretic** delivery.

51 A method in accordance with claim 49 wherein said administration is made contemporaneously with said **iontophoretic** delivery.

52 A method in accordance with claim 49 wherein said administration is made subsequent to said **iontophoretic** delivery.

53 A method in accordance with claim 28 wherein said condition is ocular inflammation...

...or irritation arising from the use of a cosmetic or sIdn care product which causes **skin** sensitization or irritation, comprising administering

an amount of a calcium channel blocker effective to reduce...

...is a sIdn
inflammatory condition.

59 A method in accordance with claim 58 wherein said **skin** inflammatory condition is a member selected from the group consisting of psoriasis, atopic dermatitis, UV-induced inflammation and contact dermatitis.
60 A method in accordance with claim 58 wherein said **skin** inflammatory condition is psoriasis.

61 A method in accordance with claim 58 wherein said sIdn inflammatory condition is atopic dermatitis.

62 A method in accordance with claim 58 wherein said **skin** inflammatory condition is contact dermatitis.

63 A method in accordance with claim 58 wherein said...

...condition is UV-induced inflammation.

64 A method in accordance with claim 58 wherein said **skin** inflammatory condition is induced by other locally applied agents.

65 A method in accordance with claim 58 wherein said **skin** inflammatory condition is induced by a drug.

66 A method in accordance with claim 58...

...and AIDS.
70 A method in accordance with claim 55 wherein said condition is a **skin**

adverse reaction associated with the application of a transdermal patch to a selected area of the **skin** , comprising administering to said selected area of the **skin** an amount of a diuretic effective to reduce said adverse reaction in conjunction with said...

...of said patch.

74 A method in accordance with claim 55 wherein said condition is **skin** sensitization and irritation associated with **iontophoretic** delivery of a therapeutic agent, comprising administering therapeutically effective amount of a diuretic in conjunction with said **iontophoretic** delivery of said therapeutic agent.

75 A method in accordance with claim 74 wherein said administration is made prior to said **iontophoretic** delivery.

76 A method in accordance with claim 74 wherein said administration is made contemporaneously with said **iontophoretic** delivery.

77 A method in accordance with claim 74 wherein said administration is made subsequent to said **iontophoretic** delivery.

78 A method in accordance with claim 55 wherein said condition is ocular inflammation...

...or irritation arising from the use of a cosmetic or sIdn care product which causes **skin** sensitization or irritation, comprising administering an amount of a diuretic effective to reduce said sensitization...sIdn

inflammatory
condition is psoriasis.

85 A method in accordance with claim 82 wherein said **skin** inflammatory condition is atopic dermatitis.

86 A method in accordance with claim 82 wherein said **skin** inflammatory condition is contact dermatitis.

87 A method in accordance with claim 82 wherein said **skin** inflammatory condition is UV-induced inflammation.

88 A method in accordance with claim 82 wherein said **skin** inflammatory condition is induced by Retin-A.
89 A method in accordance with claim 80...

...and AIDS.

92 A method in accordance with claim 80 wherein said condition is a **skin**

adverse reaction associated with the application of a transdermal patch to a selected area of the **skin** , comprising administering to said selected area of the **skin** an amount of an antidiarrheal effective to reduce said adverse reaction in conjunction with said...

...of said patch.

96 A method in accordance with claim 80 wherein said condition is **skin** sensitization and irritation associated with **iontophoretic** delivery of a therapeutic agent, comprising administering therapeutically effective amount of an antidiarrheal in conjunction with said **iontophoretic** delivery of said therapeutic agent.

97 A method in accordance with claim 96 wherein said administration is made prior to said **iontophoretic** delivery.
98 A method in accordance with claim 96 wherein said administration is made contemporaneously with said **iontophoretic** delivery.

99 A method in accordance with claim 96 wherein said administration is made subsequent to said **iontophoretic** delivery. 100. A method in accordance with claim 80 wherein said condition is ocular inflammation... induced inflammation and contact dermatitis. 105. A method in accordance with claim 103 wherein said **skin** inflammatory condition is psoriasis. 106. A method in accordance with claim 103 wherein said sIdn...

...condition is UV-induced inflammation. 109. A method in accordance with claim 103 wherein said **skin** inflammatory condition is induced by Retin-A.
110. A method in accordance with claim 102...

...and AIDS. 113. A method in accordance with claim 102 wherein said condition is a **skin** adverse reaction associated with the application of a transdermal patch to a selected area of the **skin** , comprising administering to said selected area of the **skin** an amount of a flagonist effective to reduce said adverse reaction in conjunction with said...
...of said patch. 117. A method in accordance with claim 102 wherein said condition is **skin** sensitization and irritation associated with **iontophoretic** delivery of a therapeutic agent, comprising administering therapeutically effective amount of a 0-agonist in conjunction with said

iontophoretic delivery of said therapeutic agent. 118. A method in accordance with claim 117 wherein said administration is made prior to said **iontophoretic** delivery. 119. A method in accordance with claim 117 wherein said administration is made contemporaneously with said **iontophoretic** delivery. 120. A method in accordance with claim 117 wherein said administration is made subsequent to said **iontophoretic** delivery. 121. A method in accordance with claim 102 wherein said condition is ocular inflammation...or irritation arising from the use of a cosmetic or sIdn care product which causes **skin** sensitization or irritation, comprising administering an amount of a P-agonist effective to reduce said...

...RO 201724. 125. A method in accordance with claim 123 wherein said condition is a **skin** inflammatory condition. 126. A method in accordance with claim 125 wherein said sIdn inflammatory condition...

...condition is UV-induced inflammation. 128. A method in accordance with claim 125 wherein said **skin** inflammatory condition is induced by Retin-A. 129. A method in accordance with claim 123...

...reaction associated with the application of a transdermal patch to a selected area of the **skin** , comprising administering to said selected area of the **skin** an amount of a phosphodiesterase inhibitor effective to reduce said adverse reaction in conjunction with...

...in accordance with claim 123 wherein said condition is sIdn sensitization and irritation associated with **iontophoretic** delivery of a therapeutic agent, comprising administering therapeutically effective amount of a phosphodiesterase inhibitor in conjunction with said **iontophoretic** 'delivery of said therapeutic agent. 134. A method in accordance with claim 133 wherein said administration is made prior to said **iontophoretic** delivery. 135. A method in accordance with claim 133 wherein said administration is made contemporaneously with said **iontophoretic** delivery. 136. A method in accordance with claim 133 wherein said administration is made subsequent to said **iontophoretic** delivery. 137. A method in accordance with claim 123 wherein said condition is ocular inflammation...

...said condition is sIdn sensitization or irritation arising from the use of a cosmetic or **skin** care product which causes sIdn -sensitization or irritation, comprising administering an amount of a phosphodiesterase...

```
Set     Items   Description
S1      20780   ENHANC?()AGENT? OR DMSO OR ETHANOL OR PENETRAT?()SOLVENT? -
             OR (SULPHUR? OR SULFUR?)()COMPOUND?()SOLVENT?
S2          0   RN=67-68-5
S3          0   DC=D.02.886.640.150
S4      30551   (CLARIFY? OR CLARIFI?)()AGENT? OR GLUCOSE OR GLUCONIC OR D-
             EXTROGLUCOSE OR DEXTROSE OR DEXTRONIC OR MALTONIC
S5       9689   GLYCOGEN? OR GLYCERYL? OR GLYCERIN? OR GLYCEROL?
S6          0   DC=D09.203.546.359.448
S7          0   RN=50-99-7
S8         39   DIATRIZOATE()MEGLUMINE OR DIATRIZOATE()METHLYGLUCAMINE OR -
             DIATRIZOIC()ACID()METHYLGLUCAMINE OR MEGLUMINE()DIATRIZOATE OR
              METHYLGLUCAMINE()DIATRIZOATE OR (AMIDOTRICOIC OR AMIDOTRIZOI-
             C)()ACID? OR MEGLUMINE()AMIDOTRIZOATE
S9          0   RN=131-49-7
S10         0   DC=(D02.033.800.813.550.500 OR D02.241.223.100.140.100.375-
             .880.275 OR D09.203.037.342.600.500 OR D09.203.853.813.550.50-
             0)
S11      1656   IONTOPHORE? OR IONTOTHERAP? OR IONIC()THERAP? OR EMDA OR S-
             ONOPHORE? OR ELECTROPORAT? OR ELECTRO()PORAT?
S12         0   DC=E05.300.650
S13        40   (MICRONEEDLE? OR MICRO()NEEDLE?)()ARRAY? ?
S14   4108533   INCREAS? OR ENHANC? OR AMELIORAT?
S15   2572684   PERMIT? OR PERMISS? OR ALLOW?
S16   2700931   BETTER? OR IMPROV?
S17     14514   RECEPTABIL? OR PERMEABIL? OR PERMEABL? OR LUCENCY?
S18    143699   TRANSLUCEN? OR TRANSPAREN? OR CLEARNESS OR CLARITY
S19   1028918   OPTICAL? OR LIGHT? OR LUCID?
S20    148287   PERMEAB?()(BARRIER? OR LAYER? OR STRAT?) OR SKIN
S21     20337   CONJUNCTIV? OR EPITHELI? OR SCLERA? OR STRAT?()CORNE? OR (-
             INTERSTIT? OR INTER()STIT?)()(SPACE? OR TISSUE?)
S22         0   IC=(A61N? OR A61M? OR A61B?)
S23       901   DIMETHYL()(SULFOXIDE OR SULPHONYL) OR DIMEXIDE OR RIMSO OR
             RIMSO100 OR SULFINYL()BISMETHANE OR SULFINYLBISMETHANE
S24     45493   (DRIVING OR ELECTRIC()PULSE OR ELECTRICPULSE OR ELECTROMOT-
             IVE OR ELECTRO()MOTIVE OR ACOUSTIC? OR ULTRASONIC? OR ELECTRI-
             CAL? OR RADIOFREQUENCY? OR RADIO()FREQUENCY OR TEMPERATURE OR
             THERMAL OR PHYSICAL OR CHEMICAL OR CONCENTRATION OR E...
S25        42   (S1:S3 OR S23) AND S4:S10 AND (S11:S13 OR S24)
S26        42   S25 AND S14:S21
S27        21   S25 AND S20:S21
S28        42   S26:S27
S29        21   S28 AND PY<1999
S30        20   RD (unique items)
? show files
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File 743:(New Jersey)The Record 1989-2003/Dec 04

?

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    FILE 'HCAPLUS, MEDICONF' ENTERED AT 14:46:28 ON 05 DEC 2003
L1       247304 S ENHANC? AGENT? OR DMSO OR ETHANOL OR PENETRAT? SOLVENT? OR (S
L2        26661 S 67-68-5/RN
L3        13215 S DIMETHYL (W) (SULFOXIDE OR SULPHONYL) OR DIMEXIDE OR RIMSO OR
L4       259327 S L1-L3
L5       548517 S (CLARIFY? OR CLARIFI?) (W) AGENT? OR GLUCOSE OR GLUCONIC OR D
L6       157589 S 50-99-7/RN
L7        50776 S 56-81-5/RN
L8          260 S DIATRIZOATE MEGLUMINE OR DIATRIZOATE METHYLGLUCAMINE OR DIATR
L9          290 S 131-49-7/RN
L10      562797 S L5-L9
L11       10500 S IONTOPHOR? OR IONTOTHERAP? OR IONIC THERAP? OR EMDA OR SONOPH
L12       22625 S (DRIVING OR ELECTRIC PULSE OR ELECTRICPULSE OR ELECTROMOTIVE
L13       95236 S (ELECTRICAL? OR RADIOFREQUENCY? OR RADIO FREQUENCY? OR TEMPER
L14      126099 S L11-L13
L15          78 S L4 AND L10 AND L14
L16      332898 S PERMEAB? (W) (BARRIER? OR LAYER? OR STRAT?) OR SKIN OR CONJUN
L17          10 S L15 AND L16
L18           4 S L17 AND PY<=1999
```

> display l18 1-4 abs ibib kwic

L18 ANSWER 1 OF 4 HCAPLUS COPYRIGHT 2003 ACS on STN

AB The transdermal drug delivery (TDD) system has largely been divided into phys., biochem. and chem. methods. Recently, combinations of these methods were introduced for more effective delivery with less side effects. The authors performed this study to identify the effectiveness and mechanism of TDD using the phys. method, **iontophoresis**, + the chem. method, pretreatment with chem. enhancer. The action sites of chem. enhancers in the **stratum corneum** (SC) were observed by electron microscope. The authors also studied whether this combined method synergistically impaired the **skin** barrier. To confirm the synergistic effect on **skin** penetration by this combined method, the authors measured the blood **glucose** level after insulin **iontophoresis** following a chem. enhancer pretreatment in rabbits. The results were as followed. (1) Dilatation of the intercellular lipid layers of the SC and lacunae was prominent in pretreatment with chem. enhancers inducing high transepidermal water loss (TEWL). (2) The **skin** barrier impairment, with repeated treatments showing an increased TEWL and also epidermal proliferation, was increased with the chem. enhancers that showed a high TEWL immediately after treatment. (3) The combination of chem. enhancer pretreatment and **iontophoresis** showed no synergistic impairment of the **skin** barrier. (4) The chem. enhancer pretreatment with greater impairment of the **skin** barrier could increase the delivery of insulin by **iontophoresis**. These results showed that a combination of chem. enhancer pretreatment and **iontophoresis** could deliver drugs more effectively than **iontophoresis** alone. Our proposed theory is that **iontophoretic** drug delivery may be easier through the dilated intercellular spaces of the SC which have a lower elec. impedance following the chem. enhancer pretreatment. Because the effect and the side effects in the combination are decided by the chem. enhancer rather than **iontophoresis**, the development of proper chem. enhancers is important in future plans.

ACCESSION NUMBER: 1999:705274 HCAPLUS
DOCUMENT NUMBER: 131:327446
TITLE: The pretreatment effect of chemical **skin** penetration enhancers in transdermal drug delivery using **iontophoresis**
AUTHOR(S): Choi, Eung Ho; Lee, Seung Hun; Ahn, Sung Ku; Hwang, Sang Min
CORPORATE SOURCE: Department Dermatology, Wonju College Medicine, Yonsei Univ., Wonju, 220, S. Korea
SOURCE: Skin Pharmacology and Applied Skin Physiology (**1999**), 12(6), 326-335
CODEN: SPAPFF; ISSN: 1422-2868
PUBLISHER: S. Karger AG
DOCUMENT TYPE: Journal
LANGUAGE: English
REFERENCE COUNT: 35 THERE ARE 35 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

TI The pretreatment effect of chemical **skin** penetration enhancers in transdermal drug delivery using **iontophoresis**

SO Skin Pharmacology and Applied Skin Physiology (**1999**), 12(6), 326-335
CODEN: SPAPFF; ISSN: 1422-2868

AB The transdermal drug delivery (TDD) system has largely been divided into phys., biochem. and chem. methods. Recently, combinations of these methods were introduced for more effective delivery with less side effects. The authors performed this study to identify the effectiveness and mechanism of TDD using the phys. method, **iontophoresis**, + the chem. method, pretreatment with chem. enhancer. The action sites of chem. enhancers in the **stratum corneum** (SC) were observed by electron microscope. The authors also studied whether this combined

method synergistically impaired the **skin** barrier. To confirm the synergistic effect on **skin** penetration by this combined method, the authors measured the blood **glucose** level after insulin **iontophoresis** following a chem. enhancer pretreatment in rabbits. The results were as followed. (1) Dilatation of the intercellular lipid layers of the SC and lacunae was prominent in pretreatment with chem. enhancers inducing high transepidermal water loss (TEWL). (2) The **skin** barrier impairment, with repeated treatments showing an increased TEWL and also epidermal proliferation, was increased with the chem. enhancers that showed a high TEWL immediately after treatment. (3) The combination of chem. enhancer pretreatment and **iontophoresis** showed no synergistic impairment of the **skin** barrier. (4) The chem. enhancer pretreatment with greater impairment of the **skin** barrier could increase the delivery of insulin by **iontophoresis**. These results showed that a combination of chem. enhancer pretreatment and **iontophoresis** could deliver drugs more effectively than **iontophoresis** alone. Our proposed theory is that **iontophoretic** drug delivery may be easier through the dilated intercellular spaces of the SC which have a lower elec. impedance following the chem. enhancer pretreatment. Because the effect and the side effects in the combination are decided by the chem. enhancer rather than **iontophoresis**, the development of proper chem. enhancers is important in future plans.

ST chem enhancer **iontophoresis** transdermal drug delivery

IT **Iontophoresis**
(pretreatment effect of chem. **skin** penetration enhancers in transdermal drug delivery using **iontophoresis**)

IT Drug delivery systems
(transdermal; pretreatment effect of chem. **skin** penetration enhancers in transdermal drug delivery using **iontophoresis**)

IT 57-55-6, Propylene glycol, biological studies 60-33-3, Linoleic acid, biological studies 64-17-5, **Ethanol**, biological studies 112-80-1, Oleic acid, biological studies
RL: BAC (Biological activity or effector, except adverse); BSU (Biological study, unclassified); THU (Therapeutic use); BIOL (Biological study); USES (Uses)
(pretreatment effect of chem. **skin** penetration enhancers in transdermal drug delivery using **iontophoresis**)

L18 ANSWER 2 OF 4 HCAPLUS COPYRIGHT 2003 ACS on STN

AB The in vitro elec. properties of human **skin** were investigated in various solvents and salt concns., using electrochem. methods, in relation to to **iontophoretic** drug delivery. Increasing **ethanol** concentration in aqueous **ethanol** could increase the porosity of **skin**, whereas aqueous **glycerol** and aqueous propylene glycol containing up to 50% solvent did not not produce appreciable changes. When a current was applied, the steady-state elec. resistance of **skin** was constant at low currents, and decreased with increasing currents. This behavior reflected a transition of transport mechanism, from conduction and diffusion controlled to convection. The presence of electroosmosis supports previous findings that ions are transported through charged and narrow pathways.

ACCESSION NUMBER: 1994:663650 HCAPLUS
DOCUMENT NUMBER: 121:263650
TITLE: Salt concentration and solvent effects on the in vitro electrical resistance of human **skin**
AUTHOR(S): Dinh, Steven M.; Kachmar, Deborah A.
CORPORATE SOURCE: Basic Pharmaceutics Research, CIBA-GEIGY Corporation, Ardsley, NY, 10502, USA
SOURCE: Polymeric Materials Science and Engineering (**1993**), 70, 84-5
CODEN: PMSEDG; ISSN: 0743-0515
DOCUMENT TYPE: Journal
LANGUAGE: English

TI Salt concentration and solvent effects on the in vitro electrical resistance of human **skin**

SO Polymeric Materials Science and Engineering (**1993**), 70, 84-5
CODEN: PMSEDG; ISSN: 0743-0515

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ST **skin** elec resistance salt solvent **iontophoresis**

IT **Iontophoresis**
Skin
Solvent effect
(salt concentration and solvent effects on in vitro elec. resistance of human
skin in relation to **iontophoresis**)

IT Salts, biological studies
RL: BPR (Biological process); BSU (Biological study, unclassified); THU (Therapeutic use); BIOL (Biological study); PROC (Process); USES (Uses)
(salt concentration and solvent effects on in vitro elec. resistance of human
skin in relation to **iontophoresis**)

IT Electric activity
(resistance, salt concentration and solvent effects on in vitro elec. resistance of human **skin** in relation to **iontophoresis**
)

IT Pharmaceutical dosage forms
(topical, salt concentration and solvent effects on in vitro elec. resistance
of human **skin** in relation to **iontophoresis**)

L18 ANSWER 3 OF 4 HCAPLUS COPYRIGHT 2003 ACS on STN

AB In vitro **iontophoretic** transdermal delivery (ITD) at a continuous c.d. of 0.1 mA/cm2 of cromolyn sodium (CS) across hairless guinea pig **skin** (HGP) was studied with and without enhancers. CS was quantitated by a sensitive HPLC method. At a saturated drug concentration of CS in 80:20 mixture of **ethanol**/6.66 mM acetate buffer, an overall flux enhancement compared to buffer alone was observed This enhancement was determined to be an additive effect of **iontophoresis** and **ethanol**. Chem. enhancers, such as anionic surfactants (e.g. sodium dodecyl sulfonate and sodium lauryl sulfate), inhibited the permeation of CS ions at concentration less than or equal to the critical micelle concentration No significant change in flux ($P > 0.05$) was observed when propylene glycol was added at different concns. to yield solns. with varying dielec. consts. in the aqueous donor medium. Aqueous **glycerol** solution was ineffective for ITD. Conducting gels of ionic polymers, Polyjel HV and Lubrijel MS, decreased the flux of CS significantly ($P < 0.05$). Nonionic polymers such as hydroxypropyl cellulose (Klucel-LF) and polyvinyl alc. did not affect the flux and may be used for ITD of CS from a transdermal patch. An optimized solution formulation for CS was incorporated in a com. available electropatch, from which delivery rates up to 46 ± 5 μg/cm2h-1. were achieved. The optimized formulation of CS provided about 18 fold higher flux compared to an unoptimized formulation from the electropatch. Stainless steel or Ag/AgCl electrodes showed no difference

in the flux of CS from the patch. Therapeutic levels of CS in humans may be achieved by this modern non-invasive drug-delivery route.

ACCESSION NUMBER: 1994:663516 HCAPLUS
DOCUMENT NUMBER: 121:263516
TITLE: Effect of chemical enhancers and conducting gels on **iontophoretic** transdermal delivery of cromolyn sodium
AUTHOR(S): Gupta, Sanjeev K.; Kumar, Saran; Bolton, Sanford; Behl, Charanjeet R.; Waseem Malick, A.
CORPORATE SOURCE: Nutley, NJ, 07110, USA
SOURCE: Journal of Controlled Release (**1994**), 31(3), 229-36
CODEN: JCREEC; ISSN: 0168-3659
DOCUMENT TYPE: Journal
LANGUAGE: English

TI Effect of chemical enhancers and conducting gels on **iontophoretic** transdermal delivery of cromolyn sodium

SO Journal of Controlled Release (**1994**), 31(3), 229-36
CODEN: JCREEC; ISSN: 0168-3659

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ST cromolyn transdermal delivery conducting gel **iontophoresis**; penetration enhancer cromolyn transdermal delivery gel

IT Polyelectrolytes
Skin
(conducting gels and penetration enhancers for **iontophoretic** transdermal delivery of cromolyn sodium)

IT Surfactants
(anionic, conducting gels and penetration enhancers for **iontophoretic** transdermal delivery of cromolyn sodium)

IT Pharmaceutical dosage forms
(gels, controlled-release, conducting gels and penetration enhancers for **iontophoretic** transdermal delivery of cromolyn sodium)

IT Pharmaceutical dosage forms
(transdermal, conducting gels and penetration enhancers for **iontophoretic** transdermal delivery of cromolyn sodium)

IT 28474-30-8, Poly(**glyceryl** methacrylate)
RL: THU (Therapeutic use); BIOL (Biological study); USES (Uses)
(Lubrijel MS; conducting gels and penetration enhancers for

iontophoretic transdermal delivery of cromolyn sodium)

IT **56-81-5, Glycerol**, biological studies 57-55-6, Propylene glycol, biological studies 64-17-5, **Ethanol**, biological studies 151-21-3, Sodium lauryl sulfate, biological studies 2386-53-0, Sodium dodecyl sulfonate 9002-89-5, Polyvinyl alcohol 9004-64-2, Klucel-L 15826-37-6, Cromolyn sodium 142444-14-2, Polyjel HV
RL: THU (Therapeutic use); BIOL (Biological study); USES (Uses)
(conducting gels and penetration enhancers for **iontophoretic** transdermal delivery of cromolyn sodium)

L18 ANSWER 4 OF 4 HCAPLUS COPYRIGHT 2003 ACS on STN

AB A new and improved method is disclosed for the transdermal administration of agents using **iontophoresis** in conjunction with a water-soluble **stratum corneum**-lipid modifier (lactam, ester, alc., amide, etc.). The lipid modifier may be used prior to **iontophoresis** or simultaneously with it. There may also be optionally present a water. soluble polar compound (glycol, urea, etc.). Compns. and articles useful in the processes of the invention are also provided. Use of 2-n-nonyl-1,3-dioxolane as a lipid modifier in conjunction with **iontophoresis** increased flux and amount of transdermal delivery of indomethacin.

ACCESSION NUMBER: 1993:588585 HCAPLUS
DOCUMENT NUMBER: 119:188585
TITLE: **Stratum corneum**-lipid modifier in improved **iontophoretic** administration of drugs
INVENTOR(S): Samour, Carlos M.; Eisenberg, Solomon R.
PATENT ASSIGNEE(S): Macrochem Corp., USA; Boston University
SOURCE: Eur. Pat. Appl., 26 pp.
CODEN: EPXXDW
DOCUMENT TYPE: Patent
LANGUAGE: English
FAMILY ACC. NUM. COUNT: 1
PATENT INFORMATION:

PATENT NO.	KIND	DATE	APPLICATION NO.	DATE	
EP 552879	A1	19930728	EP 1993-300198	19930113	<--
EP 552879	B1	19980819			
R: AT, BE, CH, DE, DK, ES, FR, GB, GR, IT, LI, LU, NL, PT, SE					
AT 169826	E	19980915	AT 1993-300198	19930113	<--
ES 2120477	T3	19981101	ES 1993-300198	19930113	<--
CA 2087679	AA	19930722	CA 1993-2087679	19930120	<--
JP 05339170	A2	19931221	JP 1993-23532	19930120	<--
US 5527797	A	19960618	US 1993-109599	19930820	<--

PRIORITY APPLN. INFO.: US 1992-823380 19920121
OTHER SOURCE(S): MARPAT 119:188585
TI **Stratum corneum**-lipid modifier in improved **iontophoretic** administration of drugs
PI EP 552879 A1 **19930728**

PATENT NO.	KIND	DATE	APPLICATION NO.	DATE	
PI EP 552879	A1	19930728	EP 1993-300198	19930113	<--
EP 552879	B1	19980819			
R: AT, BE, CH, DE, DK, ES, FR, GB, GR, IT, LI, LU, NL, PT, SE					
AT 169826	E	19980915	AT 1993-300198	19930113	<--
ES 2120477	T3	19981101	ES 1993-300198	19930113	<--
CA 2087679	AA	19930722	CA 1993-2087679	19930120	<--
JP 05339170	A2	19931221	JP 1993-23532	19930120	<--
US 5527797	A	19960618	US 1993-109599	19930820	<--

AB A new and improved method is disclosed for the transdermal administration of agents using **iontophoresis** in conjunction with a water-soluble **stratum corneum**-lipid modifier (lactam, ester, alc.,

amide, etc.). The lipid modifier may be used prior to **iontophoresis** or simultaneously with it. There may also be optionally present a water. soluble polar compound (glycol, urea, etc.). Compns. and articles useful in the processes of the invention are also provided. Use of 2-n-nonyl-1,3-dioxolane as a lipid modifier in conjunction with **iontophoresis** increased flux and amount of transdermal delivery of indomethacin.

ST **stratum corneum** lipid modifier **iontophoresis**

IT Acetals
Alcohols, biological studies
Amides, biological studies
Carboxylic acids, biological studies
Esters, biological studies
Lactams
RL: BIOL (Biological study)
(as **stratum corneum**-lipid modifiers, for **iontophoresis**)

IT Carbonates, biological studies
RL: BIOL (Biological study)
(cycloalkylene, as **stratum corneum**-lipid modifiers, for **iontophoresis**)

IT Lipids, biological studies
RL: BIOL (Biological study)
(of **stratum corneum**, modifiers, for **iontophoresis**)

IT Glycols, biological studies
RL: BIOL (Biological study)
(**stratum corneum**-lipid modifier and, for **iontophoresis**)

IT **Iontophoresis**
(**stratum corneum**-lipid modifier for)

IT Alcohols, compounds
Carboxylic acids, esters
RL: BIOL (Biological study)
(ethoxylated, as **stratum corneum**-lipid modifiers, for **iontophoresis**)

IT Acetals
RL: BIOL (Biological study)
(hemi-, as **stratum corneum**-lipid modifiers, for **iontophoresis**)

IT Molecules
(polar, **stratum corneum**-lipid modifier and, for **iontophoresis**)

IT **Skin**
(**stratum corneum**, lipid modifier for, for **iontophoresis**)

IT 2687-96-9, N-Dodecyl pyrrolidone 4353-06-4, 2-n-Nonyl-1,3-dioxolane 55257-88-0 59227-89-3, N-Dodecyl caprolactam
RL: BIOL (Biological study)
(as **stratum corneum**-lipid modifier, for **iontophoresis**)

IT 3515-94-4, 2-Pentyl-1,3-dioxolane 5421-12-5, 2-Nonyl-4-methyl-1,3-dioxolane 6316-55-8 66512-92-3 150460-70-1
RL: PROC (Process)
(as **stratum corneum**-lipid modifier, indomethacin **iontophoretic** delivery in presence of)

IT 64-18-6D, Formic acid, esters 110-91-8D, Morpholine, derivs. 505-22-6D, 1,3-Dioxane, derivs. 646-06-0D, 1,3-Dioxolane, derivs.
RL: BIOL (Biological study)
(as **stratum corneum**-lipid modifiers, for **iontophoresis**)

IT 53-86-1, Indomethacin
RL: BIOL (Biological study)
(**iontophoretic** delivery of, **stratum corneum**

-lipid modifier effect on)

IT **50-99-7**, D-**Glucose**, biological studies 57-13-6, Urea, biological studies 75-12-7, Formamide, biological studies 646-06-0, Dioxolane 3812-32-6, Carbonate, biological studies
RL: BIOL (Biological study)
(**stratum corneum**-lipid modifier and, for **iontophoresis**)

IT 58218-95-4, Propylene glycol-**ethanol** mixture
RL: BIOL (Biological study)
(**stratum corneum**-lipid modifier and, indomethacin **iontophoretic** delivery in presence of)